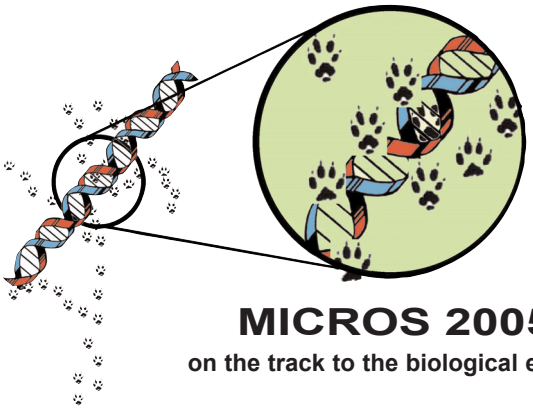

MICROS 2005

on the track to the biological effects

14th International Symposium on Microdosimetry

An Interdisciplinary Meeting on
Ionising Radiation Quality, Molecular Mechanisms, Cellular Effects, and Their Consequences for Low Level Risk Assessment and Radiation Therapy

November 13-18, 2005
Venezia, Italy

Programme and Abstracts

INFN Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro and Sezione INFN di Pavia

Dipartimento di Fisica Nucleare e Teorica
Università degli Studi di Pavia

NASA

Space Radiation Health Project NASA

CERN

MRC Medical Research Council

14th Symposium on Microdosimetry

An Interdisciplinary Meeting on

Ionising Radiation Quality, Molecular Mechanisms, Cellular Effects, and Their Consequences forLow Level Risk Assessment and Radiation Therapy

November 13 – 18, 2005
Venezia – Italy

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Peter O'Neill - *MRC-Radiation and Genome Stability Unit, Harwell, UK*
Andrea Ottolenghi - *University of Pavia and INFN, Pavia, Italy*

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Organized by:

INFN - Laboratori Nazionali di Legnaro, Legnaro-Padova, Italy

Università degli Studi di Pavia, Dipartimento di Fisica Nucleare e Teorica and INFN Pavia, Italy

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Regione Veneto, Italy

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Investigators Travel Award

ANDREEV	**Sergey**	***Russia***
BOISSIERE	**Arnaud**	***USA***
CORNELIUS	**Iwan**	***Australia***
CZUB	**Joanna**	***Poland***
De BACCO	**Francesca**	***Italy***
ELSASSER	**Thilo**	***Germany***
FILIMONOVA	**Galina**	***Russia***
GARTY	**Guy**	***USA***
JADRNICKOVA	**Iva**	***Czech Rep***
KABAKOV	**Alexander**	***Russia***
MANIOU	**Zoitsa**	***UK***
MASCIALINO	**Barbara**	***Italy***
MORO	**Davide**	***Italy***
PINTO	**Massimo**	***USA***
RENIERS	**Brigitte**	***Canada***
STISOVA	**Viktorie**	***Czech Rep***
SUVORAVA	**Tatsiana**	***Belarus***
TANNO	**Yuji**	***Japan***
TIKHONOVA	**Catherina**	***Russia***

MICROS 2005
on the track to biological effects

Scientific Programme

Sunday, November 13, 2005

15.00-18.00 **Registration at the "Centro Congressi San Servolo" – Isola di San Servolo, Venezia**

Registration Desk will remain open from Monday Nov. 14 to Friday Nov. 18 throughout the Symposium Scientific Sessions.

17.30-19.00 **Opening Ceremony**

Opening lecture: *H.H. Rossi Lecture:* **Dudley T. Goodhead, UK**
Energy deposition stochastics and track structure

Introduction: Hans Menzel

19.30 ***Welcome Party at the*** **"Centro Congressi San Servolo"**

21.00 ***Concert****, at the* "Centro Congressi San Servolo"

Monday, November 14, 2005

8.15-9.15* **Refresher Course: M. Dingfelder**, USA

Track structure: time evolution from physics to chemistry

Chair: H. Nikjoo

*[***** note: the "MICROS2005 shuttle boat" leaves at 07.55 from Venezia San Zaccaria (few minutes walking from "Piazza San Marco") to the "Centro Congressi San Servolo"]*

9.15-9.45 **Opening address**

9.45 -10.55 **Session I - BASIC MECHANISMS: physical aspects**

Chair: F. A. Cucinotta, P. Jacob

P. Sala, Italy (invited)
Simulation of nuclear interactions for basic radiobiology and applications: the FLUKA approach

M.G. Pia, Italy
Geant4 developments for microdosimetry simulation

L. Toburen, USA
Charge Transfer and Ionization by Intermediate-Energy Heavy Ions

11.00-11.30 **Coffee-Break**

11.30-13.00 **Session II - BASIC MECHANISMS: physical-chemical aspects**

Chair: O'Neill, M. Terrissol

N. J. Mason, UK (invited)
Electron induced damage of DNA and its molecular constitutents

H. Nikjoo, USA (invited)
Auger electrons – a nanoprobe for structural, molecular and cellular processes

A. Boissere, France-USA (invited)
DNA core-ionization, initial damage and cell inactivation

13.00-14.30 **Lunch at the "Centro Congressi San Servolo"**

14.30-15.40 Session III- MODELLING OF RADIATION DAMAGE

Chair: A. Chatterjee, M. Waligorski

M. Begusova Davidkova, Cz (invited)
Modification of DNA radiolysis by DNA-binding proteins. Structural aspects.

V. Stisova, Cz
Radiation damage to specific complexes of DNA with proteins: estrogen response element DNA – estrogen receptor

W. Friedland, Germany
Simulation of light ion induced DNA damage patterns

15.40 - 16.10 Coffee-Break

16.10 - 16.40 *W.R. Holley Memorial***: A. Chatterjee**, USA

The Collaborative Research with William R. Holley in Developing Theoretical Models in Radiation Biology

16.40-18.30 Session IV - DNA DAMAGE

Chair: M. Belli, S. G. Andreev

P. O'Neill, UK (invited)
Clustered DNA damage, mutations and radiation quality

J. Shay, USA (invited)
DNA Damage Signaling and Aging: Relationships to Telomeres and Telomerase

A. Peudon, France
Molecular basic data calculation for radiation transport in chromatin

M. Terrissol, France
Computer simulation of strand break yields in plasmid PBR322: DNA damage following 125I decay

Tuesday, November 15, 2005

8.15-9.15* **Refresher Course**: **P. Jeggo,** UK

DNA Damage and repair in cells and tissues

Chair: M. Frankenberg-Schwager

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9.15-10.45 **Session V – MOLECULAR AND CELLULAR CONSEQUENCES OF DNA DAMAGE**

Chair: A. Van Zeeland, M. A. Tabocchini

L. Sabatier, France (invited)
DNA repair, aging, radiosensitivity and cancer. Damage evolution at molecular and cellular levels. Role of Telomeres

C. Herskind, Germany
Changes in telomerase activity after irradiation of human peripheral blood lymphocytes in vitro

M. Frankenberg-Schwager, Germany
Mammography X-rays are as efficient as alpha particles at inducing neoplastic transformation of a human hybrid cell line.

10.45-11.15 **Coffee-Break**

11.15 -12.30 **Session VI – GENOMIC INSTABILITY, GENE EXPRESSION AND SIGNALLING**

Chair: M. E. Barcellos-Hoff, P. Jeggo

M. A. Kadhim, UK (invited)
Genomic instability and possible role of radiation quality

C. Limoli, USA
Interplay between oxidative stress and ionizing radiation: Modifying early and late effects in irradiated cells and tissues

J. Lu-Helsemman, Germany
Influences of *TP53* expression on cellular radiation responses and its relevance to diagnostic biodosimetry response for radiation disaster and mission environmental monitoring

12.30 Lunch at the "Centro Congressi San Servolo"

14.00-16.00 Session VII – LOW-DOSE AND NON TARGETED EFFECTS

Chair: C. Geard, O. Belyakov

F. Ballarini, Italy (invited)
Modelling approaches in investigating cell communication and bystander effects following irradiation

M. Pinto, USA
Bystander responses in human three-dimensional cultures containing radiolabeled and unlabeled cells

O. Sedelnikova, USA
Exposure of target cells to ionizing radiation induces DNA double-strand breaks in bystander cells in culture and in human tissue models

A. Kassis, USA
Inhibitory (I-125) and Stimulatory (I-123) Bystander Effects are Differentially Produced by Radiolabeled Tumor Cells: in vitro and in vivo Studies

N. Metting , USA(invited)
Overview of the U.S. DOE Low Dose Radiation Research Program

16.00 - 16.30 Coffee-Break

16.30 -18.30 Session VIII - POSTER SESSION

(Presentation of the posters with odd numbers)

Wednesday, November 16, 2005

8.15-9.15* **Refresher Course**: **O. Sapora,** Italy

Cellular signal transduction and transmission: mechanisms and role

Chair: M. A. Kadhim

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9.15 -10.45 Session IX – MICROBEAMS FOR LOW-DOSE EFFECTS STUDIES

Chair: S. Marino, B. Fisher

S. Gerardi, Italy (invited)
A comparative review of the charged particle microbeam facilities for radiobiology

G. Garty, USA
The Stand-Alone Microbeam at Columbia University

E. Kim, Korea
An Electron Microbeam Cell-Irradiation System at KIRAMS: Performance and Preliminary Experiments

Y. Tanno, Japan
The Study of Abnormal Cell Cycle Progression Caused by X-ray Microbeam Using EGFP-tagged Aurora Kinase B

10.45 - 11.15 Coffee-Break

11.15-12.35 Session X – RADIATION CARCINOGENESIS

Chair: H. Paretzke, D. J. Brenner

H. Fakir, Austria
Incorporation of microdosimetric concepts into a biologically-based model of radiation carcinogenesis

S. Andreev, Russia
Mechanistic modelling of genetic and epigenetic events in radiation carcinogenesis

H. Bijwaard, Netherland
Mechanistic models of bone cancer induction by radium and plutonium in animals compared to humans

P. Jacob, Germany
Lung cancer among Mayak workers

12.45 **Lunch at the "Centro Congressi San Servolo"**

14.30-18.00 **Social Tour** *(departure from San Servolo Isle, **14:00**)*

Thursday, November 17, 2005

8.15-9.15* **Refresher Course: G. Pantelias,** Greece

Cytogenetic methods for biodosimetry and individualization of risk after exposure to ionizing radiation

Chair: B. Loucas

[*note: the "MICROS2005 shuttle boat" leaves at 07.55 from Venezia San Zaccaria (few minutes walking from "Piazza San Marco") to the "Centro Congressi San Servolo"]

9.15-10.30 **Session XI– PHYSICS AND RADIOBIOLOGY FOR SPACE RADIATION PROTECTION**

Chair: W. Schimmerling, J. Kiefer

F.A. Cucinotta, USA (invited)
Computational Biology in Space Radiation Risk Assessments

W. Schimmerling, USA
Dose and Dose Rate Effectiveness of Space Radiation

A. Ponomarev, USA
Nuclear Fragmentation and the Number of Particle Tracks in Tissue

10.30-11.00 **Coffee-Break**

11.00-13.00 **Session XII – PROGRESS IN EXPERIMENTAL MICRODOSIMETRY**

Chair: P. Colautti, J. Dicello

X.Q. Lu, USA
Microdosimetric Analysis of RBE Dose Dependence for High LET Radiation

P. Olko, Poland
Microdosimetric Modelling of Response of Thermoluminescence Detectors to Low- and High-LET Ionising Radiation

A. Pola, Italy
A solid state microdosimeter based on a monolithic silicon telescope

B. Grosswendt, Germany
Nanodosimetry, the metrological tool for connecting radiation physics with radiation biology

V. Bashkirov, USA
Ion-counting Nanodosimeter with Particle Tracking Capabilities

E. Brauer-Krisch, France
3D Microdosimetry for Microbeam Radiation Therapy (MRT)

13.00-14.30 Lunch at the "Centro Congressi San Servolo"

14.30 - 16.00 Session XIII - PARTICLE RADIOTHERAPY

Chair: M. Scholz, L. Lindbord

D. J. Brenner, USA (invited)
Has microdosimetry contributed to progress in radiation medicine?

A. Wambersie, Belgium (invited)
The RBE issues in ion-beam therapy: some conclusions of a joint ICRU/IAEA effort relative to quantities and units

M.P.R. Waligorski, Poland
A simple track structure model of ion beam radiotherapy

16.00-16.30 Coffee-Break

16.30 -18.30 Session XIV - POSTER SESSION

(Presentation of the posters with even numbers)

20.30 Social Dinner at the "Locanda Cipriani" on the Torcello Isle

Friday, November 18, 2005

8.15-9.15* **Refresher Course: A. Waker,** Canada

Techniques for Radiation Measurements: Dosimetry and Microdosimetry

Chair: P. Olko

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9.15-10.45 **Session XV– RISK ASSESSMENT**

Chair: W. Hofmann, N. Metting

M.H. Barcellos-Hoff, USA (invited)
A systems biology approach to multicellular and multi-generational radiation responses

R. Howell, USA (invited)
Prediction of biological responses to incorporated radioactivity

L. Redpath, USA (invited)
Health risks of low photon energy imaging

10.45-11.15 **Coffee-Break**

11.15-12.30 **Session XVI**

Pannel Discussion :

Upgrading of Microdosimetry concept from "Stresa to Venezia" in risk assessment and radiation therapy
Discussants: D. Brenner (USA)**, D.T. Goodhead** (UK)**, H. Menzel** (CERN), **H. Paretzke** (Germany)**, A. Wambersie** (Belgium)

Chair: D.T. Goodhead

12.30 – 12.45:

Opportunities offered by the EC-Contract "EURONS" at the INFN - Laboratori Nazionali di Legnaro

E. Fioretto, *INFN-LNL, Italy*

12.45 –13.00 Symposium Closure

13.00 -14.30 Lunch at the “Centro Congressi San Servolo”

Satellite Meetings

Monday, November 14, 2005

18.30-20.30 **COST meeting – WP5**

(Centro Congressi San Servolo, "Auditorium")

Tuesday, November 15, 2005

18.30-20.30 **RISC-RAD board – WP5**

(Centro Congressi San Servolo, "Auditorium")

Friday, November 18, 2005

13.00-15.00 **"Low dose Reasearch" meeting: RISC-RAD board, DoE Officer, EC Officer**

(Centro Congressi San Servolo; meeting room "n.6")

15.00-18.30 **RISC-RAD ROUND TABLE** (***OPEN TO EVERYBODY!***) **on**:

"MICRO DOSES: MICRO EFFECTS? "

(Centro Congressi San Servolo, "Auditorium")

RTN-MC CELLION project: **Ph.D. students training course**

(Centro Congressi San Servolo, "Museum" meeting room)

20.00-24.00 **RISC-RAD board meeting**

(Hotel Ala San Marco, Venezia; "meeting room")

Saturday, November 19, 2005

08.30-18.30 **RISC-RAD WP2**

(Hotel Ala San Marco, Venezia; "meeting room")

ORAL
PRESENTATIONS

TRACK STRUCTURE: TIME EVOLUTION FROM PHYSICS TO CHEMISTRY

Michael Dingfelder

Department of Physics, East Carolina University, Howell Science Complex, Greenville, NC 27858, USA

Track structure simulations are a useful tool in Radiation Biology to provide information on the production of radiation damage to DNA and other cellular structures. Track structure simulations follow primary as well as secondary particles from interaction to interaction, from starting energies down to total stopping. Direct ionizations can produce direct hits or damage to the DNA and the surrounding water shell (physical stage). Radicals produced in the surrounding water (chemical stage) can also attack DNA and bases; this leads to indirect hits or damage.
Most Monte Carlo track structure codes use liquid water as substitute for soft tissue. Therefore we review and discuss interaction cross sections of charged particles (electrons, protons, light ions) with liquid water. We discuss the spatial distributions of energy depositions. We also discuss the water radiolysis and the production and transport of radicals. At the end of the talk we discuss newer developments like cross section calculations for biomolecules, DNA components and bases.

This work is supported by NASA Grant NNJ04HF39G.

SIMULATION OF NUCLEAR INTERACTIONS FOR BASIC RADIOBIOLOGY AND APPLICATIONS: THE FLUKA APPROACH

P.R Sala for the FLUKA collaboration

INFN Milano, via Celoria 16 I20133 Milano Italy

The modeling of hadron and ion transport and interactions in matter is a subject of growing interest in dosimetry and radiobiology, mainly due to the strong development of applications related to hadron therapy and space dosimetry. The nuclear reaction models embedded in the FLUKA code cover hadron-, ion- and photon-induced nuclear interactions from energies as low as few tens of MeV up to several tens of TeV. Fluka deals also with transport and interactions of electromagnetic particles and low energy neutrons, allowing for fully integrated simulations of mixed fields effects.
On-line integration of results from event-by-event track structure simulations at the nm level allows for calculation of "biological dose" (defined as DNA damage yields per cell in a given organ), in parallel with more standard LET-based evaluations.
A short description of the FLUKA hadron and ion interaction models is given, as well as comparisons with experimental data. Examples of applications are also presented.

GEANT4 DEVELOPMENTS FOR MICRODOSIMETRY SIMULATION

Maria Grazia Pia

INFN - GE, Via Dodecaneso 33, 16146, Genova, Italy

Geant4 is an object oriented toolkit for the simulation of particle interactions with matter. It provides advanced functionality for all the domains of detector simulation: Geometry, Tracking, Detector Response, Run, Event and Track management, Visualisation and User Interface, and is complemented by a rich set of physics processes, articulated through a wide choice of models. Geant4 is used by a large experimental community in many multi-disciplinary applications in high energy and nuclear physics, space science and astrophysics, medical physics, radiation protection etc.
A project, named Geant4-DNA, is in progress to extend Geant4 functionality to simulate the biological effects of radiation at the cellular and DNA level. It is sponsored by the European Space Agency (ESA) and is pursued by a multidisciplinary team of biologists, physicians, physicists, space scientists and software engineers. Geant4-DNA exploits advanced software technology to offer specific functionality for radiobiology studies in the powerful simulation environment of the Geant4 toolkit.
An overview of the project is presented, and of the perspectives for its applications and further extensions.

CHARGE TRANSFER AND IONIZATION BY INTERMEDIATE-ENERGY HEAVY IONS

L.H. Toburen, S.L. McLawhorn, R.A. McLawhorn, N. Evans, E.L. B. Justiniano, and J.L Shinpaugh

East Carolina University, Department of Physics, 27858, Greenville, USA

The use of heavy ion beams for microbeam studies of mammalian cell response leads to a need to better understand interaction cross sections for collisions of heavy ions with tissue constituents. For ion energies of a few MeV/u or less, ions capture electrons from the media in which they travel and undergo subsequent interactions as partially "dressed" ions, e.g., 16 MeV, fluorine ions have equilibrium charge 7+ and 32 MeV sulfur ions have an equilibrium charge of about 111 and as the ion energies decrease, the equilibrium charge decreases dramatically. Data for interactions of partially dressed ions are extremely rare making it difficult to estimate microscopic patterns of energy deposition leading to damage to cellular components. Such estimates, normally obtained by Monte Carlo track structure simulations, require a comprehensive data base of differential and total ionization cross sections as well as charge transfer cross sections. To provide information for track simulation we have initiated measurement of total ionization cross sections using the recoil ion method that also yields cross sections for multiple ionization processes; multiple-ionization is prevalent for heavy ion interactions. In addition, measurements of differential ionization cross sections needed for Monte Carlo simulation of detailed event-by-event particle tracks are also underway. Differential, total, and multiple ionization cross sections and electron capture and loss cross sections measured for C+ ions with energies of 100- and 200-keV/u will be described.

1S.M. Ferguson, Equilibrium Charge State Distributions of Heavy Ions in Carbon, Report ANU-P/596, The Australian National University, Canberra, 1974.

ELECTRON INDUCED DAMAGE OF DNA AND ITS MOLECULAR CONSTITUTENT

N. J. Mason*, M A Smialek, P Cahillane, S A Moore and D Mayr

Centre of Atomic, Molecular and Materials Engineering, The Open University, Walton Hall, Milton Keynes, MK7 6AA

The role of low energy secondary electrons in inducing DNA damage has only recently been recognised, despite the fact that thousands of electrons are produced as a result of ion and photon impact on cellular material. Sanche and co-workers have recently proposed a new mechanism for the production of single (SSB) and double strand breaks (DSB) of DNA at energies below those in which ionization of the molecular constituents can occur and below the energy required to liberate free radicals from the surrounding water. They demonstrated that localization of low energy electrons on the nucleotide bases, through the formation of short lived anions, can lead to molecular dissociation and thence to single and double strand breaks in the DNA. The mechanism for such anion formation by low-energy (< 20 eV) electrons arises mainly from dissociative electron attachment (DEA), producing a negative fragment accompanied by one or more associated neutral counterpart(s) e.g., e- + ABC ABC#- B- + AC or B- + A + C these neutral radical products may subsequently lead to new chemistry, inducing geno-toxicity.

In this talk I will review the rapid progress that has been made in the investigation of low energy electron interactions with biomolecular systems, in both the gaseous and condensed phase, and describe the new insights it is giving into the stability, structure and reactivity of biomolecules. I will also present some future plans to develop such studies towards even more biologically relevant media.

*Presenting author

AUGER ELECTRONS - A NANOPROBE FOR STRUCTURAL, MOLECULAR AND CELLULAR PROCESSES

Hooshang Nikjoo1,2, Peter Girard2, David E Charlton3, Charles A Laughton2

1USRA, NASA Johnson Space Center, Houston, Texas 77058, USA
2School of Pharmacy, Nottinghm University, Nottingham, NG7 2RD, UK
3 Physics Department, Concordia University, Montreal, Canada

When a neutral atom is ionized in an inner shell it is left in an excited state. The vacancy created is filled by an electron transition from a higher shell and the excess energy is released in the form of a characteristic X-ray or an electron. The latter is called an Auger electron in the honour of its discoverer Pierre Auger. The importance of Auger transitions produced following X-irradiation or the nuclear processes of K-capture and internal conversion of ?-rays in the decay of nuclides are of major interest in radiation biology. The increased evidence for this is the recent publications and proceedings of Auger Symposiums over the past 20 years. The paper reviews the recent progress in physical aspects and applications of Auger electrons in understanding molecular and cellular processes and its therapeutic potential in treatment of certain cancers. In particular, the paper presents a new application of Auger electrons, probing a class of novel DNAs whose structures are yet to be determined. Triple-stranded, or triplex, DNA is believed to occur naturally in certain gene sequences at certain times and has been postulated as a mechanism for the control of gene expression. Triplexes can also be formed artificially in certain sequences of double stranded DNA by introducing a synthetic oligonucleotide of appropriate sequence. Such oligonucleotides therefore act as vectors, and may be used to deliver DNA-interactive agents to specific gene sequences, e.g. for the artificial regulation of gene transcription. However, at present our ability to reliably bring about triplex formation is very limited, and in part this is due to the fact that we have very little information regarding the molecular structure of triplex DNA from NMR spectroscopy or X-ray crystallography. We show here that radioprobing has the potential, in theory, to greatly increase our knowledge of triplex structure, at an atomic level of detail.

DNA CORE-IONIZATION, INITIAL DAMAGE AND CELL INACTIVATION

Arnaud Boissière1, Laure Sabatier2 and Annie Chetioui3

1 Life Sciences Division, Lawrence Berkeley National Laboratory, University of California, Berkeley, California 94720, USA.
2 Laboratoire de Radiobiologie et Oncologie, CEA/DSV/DRR, B.P. N°6, 92265 Fontenay aux Roses, France.
3 Institut de Minéralogie et Physique des Milieux Condensés, Université Paris 6, CNRS UMR 7590, Campus Boucicaut, 140 rue de Lourmel, 75015 Paris Cedex, France.

There are various indications that complex lesions of DNA -especially complex DSBs- could be involved in the induction of cell inactivation and chromosomal aberration by ionizing radiation. Because of the strong energy deposition achieved locally by the inner shell ionizations, called core-ionizations, it is likely that these events, when produced on DNA, may lead to complex lesions. We propose here to review the core-model for ultra-soft X-rays -deeply studied during the last 10 years and which provides a natural explanation for the RBE variations for cell inactivation (especially around the carbon K-threshold) and provide absolute values of core efficiencies consistent with experimental data. We will also present recent results on the contribution of DNA core-ionizations event to the lethality for usual low LET radiations (fast electrons, gamma rays); we found that this core contribution is very large, of the order of 75%. This surprisingly large contribution strongly suggests new mechanisms associated with critical lesions for cell inactivation.

MODIFICATION OF DNA RADIOLYSIS BY DNA-BINDING PROTEINS. STRUCTURAL ASPECTS.

Marie Davídková1, Viktorie Štísová1, Stephane Goffinot2, Nathalie Gillard2, Bertrand Castaing2, Melanie Spotheim-Maurizot2

1Dept. of Radiation Dosimetry, Nuclear Physics Institute AS CR, Prague, Czech Republic, 2Centre de Biophysique Moléculaire CNRS, Orléans, France; davidkova@ujf.cas.cz

Binding of proteins to their cognate DNA modulates yields and locations of radiation damage of both partners. Radiolysis of DNA and proteins (free or bound) will be discussed for: 1) the E. coli lactose operator-repressor complex, 2) the complex between DNA bearing an analogue of an abasic site and the repair protein Fpg of Lactococcus Lactis.
Experimental patterns of DNA damages are presented and compared to predicted damage distribution obtained using an improved version of the stochastic model RADACK. This model takes into account both the structure of DNA and proteins and the nucleotides and amino-acids reactivity toward $OH^{\cdot}$ and $H^{\cdot}$ radicals.
At low doses proteins protect their specific binding site on DNA. At high doses, complexes are disrupted mainly trough protein damage. Loss of protein ability to bind DNA is observed at lower doses than those necessary to the disruption of the irradiated complexes. This difference is due to the protection of the proteins by the bound DNA. The loss of binding ability is the functional consequence of the amino-acids modification by $OH^{\cdot}$ radicals. Using RADACK we have identified the most probable sites of damage on the free and bound proteins. Many of the most probably damaged amino-acids are essential for the DNA-protein interaction and within complex are protected by DNA.

RADIATION DAMAGE TO SPECIFIC COMPLEXES OF DNA WITH PROTEINS: ESTROGEN RESPONSE ELEMENT DNA - ESTROGEN RECEPTOR.

1,3Viktorie Štísová, 2Stephane Goffinot, 2Melanie Spotheim-Maurizot, 3Marie Davídková,

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Binding of a protein to its specific DNA sequence is a fundamental step in the regulation of gene transcription. An exposition of DNA-protein complex to ionizing radiation may induce damage to both biomolecules and thus affect its regulatory function. Our study focuses to a complex formed by hormone response element DNA (HRE) and the recombinant human estrogen receptor alpha (ER), which mediates the signal of female sex hormones, estrogens.

The method of native polyacrylamide retardation gel electrophoresis is used to study the stability of the complex under irradiation by low LET radiation (137Cs and 60Co rays), and the ability to form the complex depending on the damage caused by ionizing radiation to each of the partners. The results indicate comparable sensitivity of DNA and receptor in the complex.

A triggering of strand breakage probability along the DNA fragment caused by ER binding is observed using the sequencing polyacrylamide gel electrophoresis. The comparison of results for free DNA and DNA with bound ER protein reveals the site of protein interaction and overall protection of DNA against radiolytic attack.

The relative probabilities of strand breaks and base damages for HRE base sequence and damages to the ER binding domain are also calculated using the Monte Carlo method-based model RADACK (Begusová et al. 2001, J. Biomol. Struct. Dyn. 19, 141). The theoretical results confirm symmetry of ER complex with palindrome HRE base sequence. The most protected against strand breakage induction is DNA in central and right part of HRE.

SIMULATION OF LIGHT ION INDUCED DNA DAMAGE PATTERNS

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The biophysical simulation code PARTRAC [1] has been used in several studies of photon, electron, proton and helium ion induced radiation effects like SSB and DSB induction, DNA fragmentation and HPRT- mutation induction. Recently, it has been extended by a new ion track module to handle ions heavier than alpha particles. Cross sections for ion-electron interactions were taken from doubly-charged helium ions of the same velocity and scaled by $Zeff^2/4$. The effective charge is determined according to the Barkas formula. This scaling law is a reasonable approximation for the simulated ions (between 3 and 36 MeV/u) heavier than He. For short transport distances between succeeding interactions the location of the second one is placed randomly from the beam line in order to limit the ionisation density below the density of water molecules. Calculations of LET values, radial dose distributions and secondary electron spectra were found in good agreement with experimental results.

DNA damage due to irradiation of human fibroblast cells by ions of boron, nitrogen and neon was calculated for energies corresponding to experimental investigations [2]. The calculations were complemented by some light isotachic ions with 5 MeV/u specific energy, by protons and He ions covering a wide range of energies as well as for 60Co and 220 kVp X-rays as reference radiation.

For these various radiation types the calculated induction of DNA damage has been analysed in various respects. In the simulation the total yield of DSB per dose shows saturation behaviour at about twice the value for low-LET radiation whereas experimental data have a decreasing tendency with increasing LET to RBE values well below 1 [2]. After application of data analysis methods used in the experimental determination of DSB yields [3] to the simulated DNA damage patterns, however, an excellent agreement for light ions was obtained. Dose dependent yields of DNA in certain size intervals and measured DNA fragment size distributions [4] were also reproduced quite well by the calculated data.

Clusters of DNA damage are supposed to be of outstanding importance for severe cellular radiation effects like inactivation and chromosomal aberrations, and possibly also for the risk of radiation induced cancer in an organism. The calculated patterns of, and energy depositions in, DNA damage clusters on a local as well as on a regional scale are analysed and their yields in relation to a reference radiation are compared to experimental data for cell inactivation [5-7]. The probability that a DNA damage cluster leads to cell inactivation is estimated from the relation of corresponding cross sections. The analysis is still in progress; results will be presented during the meeting.

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THE COLLABORATIVE RESEARCH WITH WILLIAM R. HOLLEY IN DEVELOPING THEORETICAL MODELS IN RADIATION BIOLOGY

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I have had the good fortune of working with Bill Holley for about 23 years in developing theoretical models in radiobiology. During this period I have experienced the great skills Bill possessed in understanding difficult radiobiological problems and translating them into algorithms that were very complex in nature. The results from these algorithms could then be compared with experimental data for the purpose of validation. Once validated, the algorithms could then be used to predict data from new experiments. In this presentation a review of Bill's collaborative contributions will be illustrated by giving three examples of typical radiobiological problems of great significance : (i)influence of DNA structure on the frequency of DNA fragments, (ii) clusters of DNA damage and some correlation with a few observed biological data and (iii) radiation induced chromosome aberrations. It was not known in the field of radiobiology that ionizing radiation can cause DNA damage that can result into small size DNA fragments such as 80 base pairs or smaller and a few kilo base pairs. It is the algorithm that Bill had produced that could reveal the existence of such fragment-sizes that was subsequently verified experimentally. Furthermore, the distribution of the frequencies of the size distributions supported the experimental evidence in at least one experiment that the 30nm chromatin structure is zig -zag shaped rather than solenoidal ring.

CLUSTERED DNA DAMAGE, MUTATIONS AND RADIATION QUALITY

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Clustered DNA damage, in which two or more lesions are formed within a few helical turns of DNA by a single radiation track, are induced in cellular DNA by ionising radiation. The complexity of clustered damage sites increases as the ionisation density of the radiation increases. Evidence now exists that clustered damage presents a challenge to the repair machinery, resulting in an increased probability of lesions being present at replication in cycling cells. As a consequence, these types of damage may be highly mutagenic.

Using plasmid-based methods, in which defined clustered DNA damage sites are introduced into E. coli and mutant strains deficient in base excision repair, it has been possible to study the mutability of various types of clustered DNA damage sites and gain insights into the mechanism of their processing. Evidence will be presented showing that bistranded clustered damage sites containing two base lesions or a base lesion and an abasic site are sequentially processed, thus avoiding double strand breakage. These clustered sites are highly mutagenic relative to that of the individual lesions. MutY, a post-replicative glycosylase, is important in protecting against mutations, reflecting the consequence of clustered sites being present at replication. The mutability of clusters depends not only on the relative location of lesions but also on the types of lesions present in the cluster. That clustered DNA damage sites may contribute to the deleterious health effects of radiation, especially at low doses of low LET radiation, will be discussed.

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DNA DAMAGE SIGNALING AND AGING: RELATIONSHIPS TO TELOMERES AND TELOMERASE

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Cellular senescence is a general stress-response program that restrains cellular proliferation. Under optimal growth conditions, the onset of senescence depends on telomere status. There is not a sentinel short telomere that triggers senescence but a group of about 10% of the shortest telomeres that are involved. When a minimum of two telomeres are sufficiently short (uncapped) they form non covalent end-associations leading to a DNA damage response-induced growth arrest. The global loss of the G-rich single-strand telomere overhang is not required to initiate or maintain the senescence pathway. The senescence pathway involves the formation of telomere dysfunction induced foci (TIFs) that contain DNA damage response factors, such as 53BP1, *-H2AX, and the Mre11complex. The signaling pathway responsible for establishing a senescent state in such cells involves primarily ATM, Chk1/Chk2 and p53, leading to a G1 phase arrest. Importantly, the DNA-damage response observed in senescent cells is not a transient phenomenon, but consists of a permanent activation of the DNA damage checkpoint machinery. The long-term growth arrest at senescence may be thought of as an initial anti-tumor protection mechanism.

In situations where normal cell cycle checkpoints are altered, cells can bypass the normal senescence signaling pathway and continue to grow until they reach a second growth arrest state known as crisis. In crisis, telomeres are terminally short and, in the presence of other genetic and epigenetic changes, can result in telomeric fusions, subsequent breakage-fusion-bridge cycles and in rare cells, up-regulation or reactivation of telomerase, the cellular RNP that is able to add telomeric repeats to the ends of chromosomes and thus prevent their shortening and to stably maintain telomeres. In even rarer cases crisis can be abrograted by an alternative lengthening of telomeres (ALT) pathway involving DNA recombination. In both senescence and crisis ectopic expression of the catalytic subunit of telomerase (hTERT) leads directly to an immortal state demonstrating that telomeres are important in both replicative senescence and crisis. In summary, the interconnections between cellular senescence and immortalization should help identify the molecular mechanisms underlying replicative senescence and its relationship to oncogenic transformation, both of which may be affected by long-term exposure to the spectrum of space radiation.

MOLECULAR BASIC DATA CALCULATION FOR RADIATION TRANSPORT IN CHROMATIN

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To model properly low energy radiation effect, it appears that we should work with molecular structure. We need to obtain accurately molecular binding energy of the shells and transition energies to better calculate energy transfers and depositions, as well as to simulate Auger and X-rays spectra following internal ionization.
As there are not enough experimental values for chromatin components, we have performed ab-initio calculations with GAMESS (General Atomic Molecular Electronic Structure System). We present Mulliken populations and molecular orbital binding energies for the DNA bases, the sugar-phosphate backbone and the twenty amino-acids found in histon proteins. Our values for DNA components are very similar to those published.
One of the most rigorous methods proposed to compute molecular total ionization cross section is the binary encounter dipole model, or even its approximation the Binary-Encounter-Bethe (BEB). So, we have calculated differential and integral electron impact ionization cross sections using the BEB theoretical model for all the chromatin molecules. We will show in this paper the results for the four bases, the sugar-phosphate and the twenty amino-acids. For the amino-acids, to our knowledge, it's the first attempt of that type of calculations. For DNA components, our results are in a good agreement with those found in literature.
These results are now taken into account in our CPA100 Monte-Carlo simulation code to improve the evaluation of radiation damage in chromosomes.

COMPUTER SIMULATION OF STRAND BREAK YIELDS IN PLASMID PBR322 : DNA DAMAGE FOLLOWING 125I DECAY

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Plasmid DNA has revealed of great interest in the investigations on DNA damages since, contrary to what happens in chromatin, one single break can lead to a structural deformation (as linearization event LE or relaxation event RE) that can be counted by gel electrophoresis. This has led us to improve our particle transport code with a special care of plasmid used in most of the in vivo experiments. We present results of 125I effects on plasmid pBR322 in aqueous solution, simulating the complete transport of Auger and X-rays up to the chemical phase. In addition to new sampling algorithms, we have included new BEB (Binary Encounter Bethe) cross sections for ionization by electron impact on DNA molecules, as well as new elastic cross sections computed with Independent Atom Method.
Like in experiments, we have compared the respective contributions from direct and indirect effects, running the simulations both with 125I, bound to plasmid, or free, in its vicinity. Also the influence of the hydroxyl radical scavenger DMSO has been tested, underlying that, in naked DNA, double strand breaks (caused by the decay of bound 125I) are mainly due to direct hits. The calculated yields of SSB and DSB show good agreement with experimental ones: when 125I is bound to the plasmid pBR322, we obtain 0.16 RE and 0.83 LE by decay (without DMSO). Then, when 2M DMSO is added, RE and LE probabilities become 0.22 and 0.76. The very light differences with those from literature could arise from experimental conditions.

DNA DAMAGE AND REPAIR IN CELLS AND TISSUES.

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The response to DNA damage in mammalian cells encompasses pathways of DNA repair and signal transduction responses, that impact upon cell cycle checkpoint arrest, apoptosis and aspects of repair. The most significant biological lesion induced by ionising radiation (IR) is a DNA double strand break (DSB). DSBs can be directly induced or can arise following processing or replication of other lesions, including base damage and single strand breaks. The most significant DNA DSB repair mechanism in mammalian cells is non-homologous end-joining (NHEJ), which is the major mechanism functioning in G1 but also likely functions throughout the cell cycle. Homologous recombination functions primarily to rejoin DSBs that arise at the replication fork, functioning in late S/G2. ATM-dependent signalling is the most important signal transduction mechanism that responds to a DSB. ATR-dependent signalling, which is activated by single strand regions of DNA, can also impact upon the radiation response since it can be activated by replication fork stalling and potentially at DSBs that are subject to end-resection.
Five proteins that function in the core process of NHEJ have been identified, namely Ku70, Ku80, DNA-PKcs, Xrcc4 and DNA ligase IV. In brief, the heterodimeric Ku protein binds avidly to double strand DNA ends, recruits the catalytic subunit of DNA-PK, DNA-PKcs, which in turn recruits a complex of Xrcc4 and DNA ligase IV, which effects rejoining. Mutants lacking any of these components are exquisitely radiosensitive. However, the majority of DNA ends generated by ionising radiation cannot undergo simple rejoining and require some form of end-processing. Recent studies have suggested that Artemis is a nuclease that functions in a process of end-processing a subset of DNA ends generated by ionising radiation. Artemis dependent end-processing additionally requires ATM, 53BP1, the MRN complex and H2AX. These findings demonstrate that ATM has two roles in the response to DSBs; it is required for the activation of Artemis-dependent end-processing and also activates cell cycle checkpoint arrest (and in some cell types can activate apoptosis). The DSBs repaired in an ATM/Artemis dependent manner are those normally repaired with slow kinetics in control cells and thus benefit from ATM-dependent checkpoint arrest. Artemis-defective human cells are dramatically radiosensitive demonstrating that end-processing contributes signficantly to survival to ionising radiation. In addition, PNK can also play a role in end-processing of ionising radiation induced DSBs.
The interplay between homologous recombination, NHEJ, ATM and ATR-dependent signalling in the response to ionising radiation will be discussed. These different components of the DNA damage response may play different roles in different tissues depending on the growth characteristics of the tissue and their threshold for undergoing apoptosis. The responses may also have differential impact depending upon the exposure dose, which will also be discussed.

DNA REPAIR, AGING, RADIOSENSITIVITY AND CANCER DAMAGE EVOLUTION AT MOLECULAR AND CELLULAR LEVELS ROLE OF TELOMERES

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Most of the repair of DNA damage is completed in the few hours post-irradiation. When a cell survives, mutations are believed to be fixed, "frozen", and transmitted to cell generations. Chromosome instability detected in the surviving human fibroblasts after heavy ions irradiation is characterized by end-to-end fusions involving specific chromosomes. These fusions are linked to telomere shortening associated with cell divisions. In the progeny of irradiated cells, we proposed that cells could bypass senescence signaling thus chromosome instability could progress leading to chromosome damage accumulation and to selection of chromosome imbalances that could unmask recessive genes, giving to cells a proliferative advantage. We demonstrated that the consequences of telomere loss are dramatically mutagenic for the cell, leading to: 1) chromosome instability, 2) gene amplification via the breakage/fusion/bridge (B/F/B) cycle, and 3) chromosome imbalances (gain and loss of chromosome arms) Chromosomes lacking one telomere remain unstable until they are capped. Telomere acquisition occurs mainly through Non Reciprocal Translocations (NRT) and Duplications. The loss of a single telomere can induce rearrangements not only of the chromosome that has initially lost a telomere, but in other chromosomes as well leading to karyotypic instability. These mechanistic data associated with a study of the cytogenetics of radiation-induced tumours lets us propose the following hypothetical scheme of radiation oncogenesis: a) induction of recessive gene mutations (direct effect of radiations) b) accumulation of genomic alteration in the irradiated tissues with aging and proliferation of irradiated and non irradiated cells c) unmasking, amplification… of radiation induced or pre-existing mutations due to telomere shortening d) loss of tumour suppressor functions, initiation and progression of multistage carcinogenesis.

CHANGES IN TELOMERASE ACTIVITY AFTER IRRADIATION OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES IN VITRO.

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Human telomerase consists of catalytic unit (a specialised telomerase reverse transcriptase, hTERT) and an RNA template. Recent studies have shown that ionising radiation may up-regulate telomerase activity in lymphoblastoid cell lines and further evidence suggests a role of hTERT in enhancing genomic stability and DNA repair. The purpose of the present experiments was to test whether ionising radiation may regulate telomerase activity in human peripheral blood lymphocytes (PBL). PBLs from young healthy donors were stimulated with PHA for 72 h and irradiated with doses of 1-10 Gy 6 MV x-rays. TK6 human lymphoblasts were used as controls. Telomerase activity was determined 1-4h post irradiation by the telomerase repeat amplification protocol (TRAP) with real-time PCR for quantification. Irradiation of PHA-stimulated PBL with D=2 Gy resulted in a 1.5-3.5-fold increased telomerase activity at 4h post-irradiation. The enhancement was comparable with that of TK6 lymphoblasts showing a relatively flat dose-reponse relationship. The present results show that telomerase activity can be modulated by radiation not only in cell lines but also in primary stimulated lymphocytes expressing telomerase activity. This would support a role for hTERT in the cellular radiation response and suggests telomerase activity as a possible marker for radiation exposure. Data from a clinical study of telomerase activity in radiotherapy patients are presently being analysed and will be presented.

MAMMOGRAPHY X-RAYS ARE AS EFFICIENT AS ALPHA PARTICLES AT INDUCING NEOPLASTIC TRANSFORMATION OF A HUMAN HYBRID CELL LINE

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Objective
To investigate the potential of mammography X-rays at inducing neoplastic transformation in human hybrid cells CGL1
Method
Exponentially growing cells of the human hybrid cell line CGL1 were exposed to 29 kVp mammography X-rays, 3.4 MeV alpha-particles (LET = 124 keV/ m or, for comparison, to 60-Co-gamma rays. Clonogenic survival and neoplastic transformation were determined 11 and 21 days, respectively, after irradiation. Neoplastically transformed cells were identified by the conversion of the reagent Western Blue into a water-insoluble purple/blue precipitate by alkaline phosphatase which is specifically expressed at the surface of transformed cells.
Results
The efficiency of mammography X-rays to induce cell killing is intermediate between that of 60-Co-gamma rays and alpha particles. However, mammography X-rays are as highly efficient as alpha-particles at inducing neoplastic transformation in human hybrid CGL1 cells.
Conclusion
The similar efficiency of mammography X-rays and alpha particles at inducing neoplastic transformation of human hybrid CGL1 cells should be taken into consideration for the risk estimation of mammography X-rays.

GENOMIC INSTABILITY AND POSSIBLE ROLE OF RADIATION QUALITY

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Until recently, the prevailing paradigm for radiation biology was the hit-effect relationship between nuclear irradiation and cellular effect. Recent evidence suggests that more complex global cellular responses, such as genomic instability (GI) may be operative, in irradiated and bystander cells, especially at low doses of radiation. GI is a hallmark of tumorigenic progression and is observed in the progeny of irradiated and bystander cells as the delayed and stochastic appearance of de novo chromosomal aberrations, gene mutations and delayed lethal mutations both in vitro and in vivo. It occurs at a frequency several orders of magnitude greater than would be expected for mutation in a single gene, implying that GI is a multigenic phenomenon.
The expression of GI can be influenced by genotype, cell type and radiation quality; however, the underlying mechanisms are not fully understood. While several studies have demonstrated GI induction by high and low LET radiation, our work on human and mouse primary cell systems has shown significant differences in the capacity to induce GI and the spectrum of alterations depending on LET. These differences might be attributed to differences in radiation track structure, radiation dose and radiation exposure regime (distribution of hit and un hit cells).
We shall review the role of radiation quality; describe the possible mechanisms underlining the observed differences between radiation type and present results of experiments demonstrating that the dose of low LET radiation might be the most significant factor in determining the role of radiation type in the induction of GI.

INTERPLAY BETWEEN OXIDATIVE STRESS AND IONIZING RADIATION: MODIFYING EARLY AND LATE EFFECTS IN IRRADIATED CELLS AND TISSUES

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Proliferative pools of multipotent precursor cells located in the subventricular and hippocampal dentate subgranular zones of the mammalian brain may play integral roles in the repair of the irradiated CNS. To understand the potential factors regulating their radioresponse in vivo, we have developed and characterized these cells in vitro. Our data have shown that high and low LET ionizing radiation elicits marked increases in reactive oxygen species (ROS) over acute and chronic times post-irradiation, suggesting that radiation-induced oxidative stress might be an important biochemical mechanism regulating both early and late effects in neural precursor cells. Within days following X-, proton- or 56Fe-irradiation, significant elevations (2-10 fold) in ROS levels are associated with an apoptotic depletion of neural precursor cells, mitochondrial dysfunction, lipid peroxidation, and DNA damage. These oxidative conditions have been found to persist months after irradiation and to temporally coincide with the development of neuroinflammation. We propose that cycles of oxidative stress and inflammation occur within the irradiated CNS and suppress the regeneration of neural precursors, leading to an impairment of neurogenesis and possibly cognitive function.

Related data from our lab have corroborated the importance of redox state in the metabolic homeostasis of these cells. Neural precursors exhibit extremely high levels of endogenous ROS that depend critically on the extracellular environment. These ROS have been found to impact cellular antioxidant status and growth rate. Furthermore, when these cells are subjected to exogenous or endogenous perturbations that promote a pro-oxidant environment, their radiosensitivity can be increased by 20-60% over a dose range of 1-5 Gy. Collectively, our data suggest that neural precursors are fine-tuned to respond to redox sensitive cues that dictate their response to irradiation and possibly other forms of CNS damage. Additional data will be presented highlighting how these findings might be used to overcome certain adverse sequelae in the irradiated CNS.

INFLUENCES OF TP53 EXPRESSION ON CELLULAR RADIATION RESPONSES AND ITS RELEVANCE TO DIAGNOSTIC BIODOSIMETRY RESPONSE FOR RADIATION DISASTER AND MISSION ENVIRONMENTAL MONITORING

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Introduction/Rationale: TP53 is a transcriptional activator whose targets include genes which regulate genomic stability and the cellular response to DNA damage including cell cycle progression. Ionizing radiation (IR), which causes DNA strand breaks and base damage, and UV-B, which creates cyclobutane pyrimidine dimers, photoproducts and thymine glycols in DNA, produce elevated mutation frequencies in different human cell lines, as apoptosis and necrosis. The molecular mechanism behind p53-mediated responses to IR and UV-B, i.e. growth arrest, differentiation, apoptosis and genomic instability remains unclear. For that reason, an in vitro p53 system was established in order to elucidate the functional role of p53 in different stress-reaction pathways and identify possible biological indicators.

Methods: The human leukemia cell line HL-60, which is lack of p53 gene, was stably transfected with wildtype p53 (wt-p53), mutant p53 (mut-p53) and empty control expression vectors (N). The resulting populations were treated with either ionizing radiation or UV-B and subsequently analyzed for specific radiation responses and correlated with biochemical data on protein expression.

Results: Transfection of p53 into the p53-deficient HL-60 cells resulted in suppression of cell growth and apoptotic responses. The data demonstrate that expression of p53 decreases the sensitivity to IR and UV-B in transfected HL-60 cells which indicates that apoptosis in HL-60 cells proceeds in a p53-independent manner and that p53 even appears to act protectively, by preventing apoptotic cell death. Additional experiments demonstrated that our p53 expressing HL-60 cells show markedly prolonged S- and G2 delays upon IR, as compared with their controls. Concomitantly, wt-p53 expressing HL-60 cells (as well as mut-p53 expressing HL-60 cells) show a prolonged doubling time leading to growth suppression.

Conclusion: By using our p53 minus background model system, we conclude that the tumor suppressor p53 modulates cellular radiation responses by exhibiting its functions like DNA repair, growth arrests, interfering pathway(s) of radiation-related cell death. Further evidence will be achieved in order to explore and identify specific radiation targeting genes and signals as possible biological indicators for early diagnosis of radiation damage as well as indicators for mission environmental monitoring.

MODELLING APPROACHES IN INVESTIGATING CELL COMMUNICATION AND BYSTANDER EFFECTS FOLLOWING IRRADIATION

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In the last ten years evidence has been accumulated on the so-called non-targeted effects and in particular on bystander effect, i.e. induction of damage in non-irradiated cells which respond to molecular messengers released by irradiated cells. These phenomena have been observed for different biological endpoints, both lethal (inactivation and apoptosis) and non lethal, such as mutations and transformation. Although the underlying mechanisms are largely unknown, it is clear that two types of cellular communication (i.e. via gap junctions and/or release of molecular messengers into the extracellular environment) play a fundamental role. Furthermore, more than one signal can be involved, and the effects are strongly influenced by the radiation modulating action, both on the signal release and on the cell response to the signal.
Theoretical models and simulations can be of help for improving our knowledge of the mechanisms, and for investigating the possible role of these effects in determining deviations from the linear relationship between dose and risk which is generally assumed in radiation protection. In this paper we will review different modelling approaches available in the literature. The focus will be on the different assumptions adopted by the various authors and their implications in terms of non-targeted radiobiological damage and, more generally, low-dose radiation risk. Furthermore, "critical" parameters which can modulate the model outcomes will be identified and their role will be investigated. Besides radiation dose and quality, these parameters include other factors such as cell density, medium amount, type of treatment etc. Comparisons with available experimental data will be presented, and possible implications in the fields of radiation protection and radiation therapy will be discussed.

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BYSTANDER RESPONSES IN HUMAN THREE-DIMENSIONAL CULTURES CONTAINING RADIOLABELED AND UNLABELED CELLS

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Most research on the radiation-induced bystander effect has been carried out in two-dimensional tissue culture systems. This study uses a three-dimensional model, whereby apparently normal human diploid fibroblasts (AG1522) are grown in a carbon scaffold, to investigate radiation-induced bystander effects. Cultures were pulse-labeled with 3H-deoxycytidine to selectively irradiate a minor fraction of cells, and simultaneously co-pulse-labeled with bromodeoxyuridine (BrdU) to identify the radiolabeled cells. After thoroughly washing the cultures, iododeoxyuridine (IdU) was administered and the cultures were harvested at various times thereafter. Harvested cells were stained with propidium iodide, reacted with two monoclonal antibodies specific to IdU/BrdU or BrdU respectively and subjected to multi-parameter flow cytometry. Cell-cycle progression was monitored in radiolabeled cells (BrdU+) that were chronically irradiated by low energy beta-particles emitted by 3H and in neighboring unlabeled bystander cells (BrdU-). Progression of bystander cells from G1 to S phase was measured using the iododeoxyuridine cumulative labeling index assay. As expected, radiolabeled cells were delayed, in a dose-dependent manner, in G2 and subsequently in G1. Proliferating bystander cells did not experience any G1 arrest when the radiolabeled cells were irradiated at dose rates up to 30 cGy/h. However, preliminary studies suggest that bystander cells showed measurable delayed entry into S-phase upon release from the three-dimensional culture. These preliminary studies suggest expression of a stress response in G0 bystander cells but not in bystander cells in other phases of the growth cycle.

EXPOSURE OF TARGET CELLS TO IONIZING RADIATION INDUCES DNA DOUBLE-STRAND BREAKS IN BYSTANDER CELLS IN CULTURE AND IN HUMAN TISSUE MODELS.

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That irradiated cells affect their unirradiated "bystander" neighbors is evidenced by reports of increased clonogenic mortality, genomic instability, and expression of DNA-repair genes in the bystander cell populations. The mechanisms underlying the bystander effect are obscure, but genomic instability suggests that DNA double-strand breaks (DSBs) may be involved. Formation of DSBs induces the phosphorylation of histone H2AX and this phosphorylated form, named g-H2AX, forms foci at DSB sites. We report here that the incidence of g-H2AX foci was found to increase 2.5-3.7 fold in bystander normal human fibroblasts, whether these cells were cocultured with cells targeted with microbeams or -irradiation or whether they were incubated in media conditioned on irradiated cultures. DNA DSB repair proteins accumulate at these g-H2AX foci, indicating that they are sites of DNA DSB repair. Cultured cells lack the geometric arrangement and cell-cell communication present in tissue. To determine the existence and extent of bystander effects in tissues, we examined 3-D artificial human tissue models of skin and airway (EFT-300 and Air-100, MatTek, Inc.). After cells located in a thin plane through the tissue were microbeam-irradiated, g-H2AX focus formation was measured in distal bystander cells as a function of time post-IR. Both these tissue models were found to exhibit bystander effects. The incidence of g-H2AX foci was found to increase 3.5-4.7 fold in bystander cells in both tissue models one-two days post-irradiation and remained elevated for several days. Thus, these studies demonstrate that DNA DSBs form in bystander cells of not only 2-D conventional cell culture but also locally-irradiated 3-D tissue models and that these breaks may be responsible for the downstream manifestations of the bystander effect.

INHIBITORY (125I) AND STIMULATORY (123I) BYSTANDER EFFECTS ARE DIFFERENTIALLY PRODUCED BY RADIOLABELED TUMOR CELLS: IN VITRO AND IN VIVO STUDIES.

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The radiation-induced bystander effect, originating from cells irradiated in vitro or in vivo, describes the biologic response(s) of surrounding cells not directly targeted by a radiation insult. Previously, we had demonstrated the ability of 5-[125I]iodo-2'-deoxyuridine (125IUdR)-labeled tumor cells to exert an inhibitory bystander effect (IBE) on neighboring unlabeled tumor cells growing subcutaneously in nude mice (Proc Natl Acad Sci 2002; 99:13765).

To examine further this phenomenon, we have repeated our in vivo tumor-growth studies using the Auger electron emitter 123I and compared the results with those obtained when 125I is used (the Auger electron spectra of these two radionuclides are identical but the total number of Auger electrons and the energy deposited by 125I is about twice that of 123I). We have also assessed the growth of these LS174T adenocarcinoma cells when co-incubated in vitro with either 123IUdR- or 125IUdR-labeled LS174T cells or with the supernatants obtained from four-day incubations of labeled cells.

Contrary to the IBE of 125IUdR, the presence of 123IUdR-labeled cells leads to a stimulation of cell growth both in vitro and in vivo. This stimulatory bystander effect (SBE) is seen even when the 123IUdR-labeled cells are refrigerated for several days (to allow complete decay of 123I, T1/2 = 13.3 h) prior to mixing them with unlabeled cells. Similar results are obtained when the supernatants of radiolabeled cell cultures are incubated with unlabeled tumor cells. The supernatants from 123IUdR contain increased concentrations of angiogenin, while those from 125IUdR have increased amounts of tissue inhibitors of metalloprotinases TIMP-1 and TIMP-2.

These in vitro and in vivo IBE and SBE findings (i) demonstrate the complexity of the radiobiologic principles responsible for the radiation-initiated bystander effects, (ii) significantly impact the current dogma for assessing the therapeutic potential of internally administered radionuclides, and (iii) call for a re-evaluation of the dosimetric approaches currently used for estimating the dose-response relationships in individuals after radiopharmaceutical administration or radiocontamination.

OVERVIEW OF THE U.S. DOE LOW DOSE RADIATION RESEARCH PROGRAM

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The U.S. Department of Energy Low Dose Radiation Research Program is funding basic research to determine the responses induced by radiation exposures at doses of 10cGy and lower, and at very low dose rates. This information is critical to adequately and appropriately protect people while making the most effective use of our national resources. Over the next 100 years, radiation exposures associated with human activity are expected to be low dose and low dose-rate radiation from medical tests, waste clean up, dirty bombs, and environmental isolation of materials associated with nuclear weapons and nuclear power production. The major type of radiation exposures will be low Linear Energy Transfer (LET) ionizing radiation (primarily X- and gamma-radiation) from fission products. The DOE Low Dose Radiation Research Program will thus concentrate on studies of low-LET exposures delivered at low total doses and low dose-rates. The research program is building on advances in modern molecular biology and instrumentation, not available during the previous 50 years of radiation biology research. These mechanistic studies focus on DNA damage and repair, endogenous vs. radiation-induced oxidative damage, adaptive responses, bystander effects, genomic instability and genetic susceptibility. It is also expected that radiation-induced perturbation of normal physiological processes, along with the biological system's homeostatic responses, will eventually be characterized at all levels of biological organization - from genes to cells to tissues to organisms.

CELLULAR SIGNAL TRANSDUCTION AND TRANSMISSION: MECHANISMS AND ROLE.

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The word Tranduction can be defined as the action of leading or bringing across and it has been used earlier to describe physical phenomena. More recently signal transduction is used to indicate how external influences, through specific receptors on the membrane, can determine from outside what happens inside the target cell. The receptors allow external chemical signalling molecules, the first messangers, to direct the activities of cells in a variety of ways with high specificity and precise control in terms of extent and duration. The cellular membrane is also an active component in the control of the signal transduction generating non specific signals, second messengers, and modifying the bilayer structure for enzyme activation. The first messengers and their related intracellular second messengers are controlling the metabolic pathways leading to cell survival, proliferation and differentiation. The first example of signal transduction influencing radiation response has been reported in 1974, and it will be used to describe the complete sequence of transduction and transmission events from the receptor-ligand interaction to the activation of transcription. Moreover the roles of important families of proteins (GP proteins, protein kinases and phospholipases) in intracellular signalling and their interaction with cell membranes will be discussed.

A COMPARATIVE REVIEW OF THE CHARGED PARTICLE MICROBEAM FACILITIES FOR RADIOBIOLOGY

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At the low doses (and low dose rates) of relevance to environmental and occupational radiation exposure, cancer risk assessment deserves particular attention. Epidemiological studies do not have sufficient statistical power to detect directly cancer risk associated with small doses of ionizing radiation. At these dose levels, individual cells only rarely experience traversal by densely ionizing particles, the intervals between the tracks typically being months or years. The biological effects of exactly one particle are unknown because, due to the random Poisson distribution of tracks, this cannot be simulated in vitro by conventional broad-beam exposures. Charged particle microbeam facilities are a unique tool which allows the targeting of single cells and the analysis of the induced damage on a cell-by-cell basis. In the last few years, many charged particle microbeam facilities for radiobiology came into operation or are under development worldwide. Different experimental designs have been adopted at various laboratories regarding the achievement of micrometer (or sub-micrometer) ion beam size (by mechanical collimation or magnetic focusing), particle detection, and cells recognition and positioning systems. The different approaches are reviewed and discussed.

THE STAND-ALONE MICROBEAM AT COLUMBIA UNIVERSITY

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The stand-alone microbeam at Columbia University presents a novel approach to biological microbeam irradiation studies. Foregoing a conventional accelerator as a source of energetic ions, we use a small, high-specific-activity, alpha emitter. Alpha particles emitted from this source are focused using a compound magnetic lens consisting of 24 permanent magnets arranged in two quadrupole triplets.
Using a "home made" 5 mCi Polonium source, a 1 alpha particle/sec, 10 micron diameter microbeam can be realized. As the alpha source energy is constant, once the microbeam has been set up, no further adjustments are necessary apart from a periodic replacement of the source. The use of permanent magnets eliminates the need for bulky power supplies and cooling systems required by other types of ion lenses and greatly simplifies operation. It also makes the microbeam simple and cheap enough to be realized in any large lab. We present here the Microbeam design as well as first biological results obtained with it.

AN ELECTRON MICROBEAM CELL-IRRADIATION SYSTEM AT KIRAMS: PERFORMANCE AND PRELIMINARY EXPERIMENTS

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A new electron microbeam system has been installed at Korea Institute of Radiological and Medical Sciences to be utilized for individual cell irradiation. The system components include an electron gun operating at 1 to 100 keV, a beam transport chamber delivering a micron-sized beam, a cell image acquisition and positioning part and the system control section. The present choice of source beam energy is 30 keV so that the beam enters target cells with the minimum spatial dispersion. The influence of the surrounding magnetic field on the beam track has been minimized by lining the material of high permeability inside the beam transport chamber. The beam is now available at 5 m in diameter, but can be changed in the range of 1 m to 200 m in diameter. The cells plated on the Mylar-bottomed dish are recognized by 95 % when stained but by 70 % with no stain. The step-wise positioning of target cells onto the beam leads to 0.5 m/mm in error. The system can manage to irradiate 30,000 cells per hour. The system operation has been demonstrated by delivering 5 Gy of dose to the lung cancer cells and observing ROS production in the hit cells. Beam delivery at 0.2 Gy is accomplished with 25 % of standard deviation in cellular dose.

THE STUDY OF ABNORMAL CELL CYCLE PROGRESSION CAUSED BY X-RAY MICROBEAM USING EGFP-TAGGED AURORA KINASE B

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Recently, spindle checkpoint and DNA damage checkpoint have been shown to induce mitotic arrest in response to DNA-damaging agents. However, mitotic arrest induced by ionizing radiation has been poorly understood in this stage. In this study, the effect of X-rays on mitotic cells was investigated in detail with the method of microbeam irradiation. The microbeam irradiation was carried out in the beam-line 27B in PF, KEK (Tsukuba). HeLa cells expressing EGFP-tagged Aurora kinase B was used all through this study. Each stage in M phase can be indicated with EGFP-Aurora B and microbeam irradiation was done focusing to the nucleus of each cell in each stage in M phase. Ten Gy microbeam X-rays (5.35 keV, about 20 Gy/min, 10 micron square) were irradiated to each cell. The cells under fluorescent microscope were at 35±1 oC using special heating system. Thus the cell cycle progression without X-ray irradiation could be normally observed and the cell cycle arrest at M phase after irradiation with X-ray microbeam was also observed significantly. The cell cycle progressing time from prophase to telophase was about 1 hour. On the other hand, prophase, prometaphase, or metaphase cells with 10 Gy X-ray irradiation showed transient metaphase arrest, and metaphase/anaphase transition was delayed for about 1 hour. The cells irradiated in anaphase or telophase progressed at normal speed. From these results, it is suggested that X rays affect the timing of chromosome segregation and elongates M phase. Now we are investigating the mechanism of mitotic arrest focused on spindle checkpoint and DNA damage checkpoint.

INCORPORATION OF MICRODOSIMETRIC CONCEPTS INTO A BIOLOGICALLY-BASED MODEL OF RADIATION CARCINOGENESIS

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In the biologically-based state-vector model of radiation carcinogenesis (SVM), transition rates between the various initiation and promotion stages are expressed in terms of dose (or dose rate). While the model has been successfully applied to in vitro transformation data for defined LET values, in vivo exposure to radon progeny in the human lung is characterized by a wide range of LET values in sensitive target cells. Thus to relate energy deposition at the cellular level to the interaction of single alpha particle traversals, the SVM has to be reformulated by replacing dose with hit frequency and expressing transition rates as functions of LET.
In the present work, the SVM model has been extended by incorporating microdosimetric concepts to characterize the interaction of radon progeny alpha particles with target cell nuclei. Hit frequencies and LET spectra of radon progeny alpha particles in bronchial target cells are computed for specific exposure conditions. Transition rates of the initiation stages are expressed as functions of LET by describing the complexity of DNA double strand breaks by cluster formation analysis and their interaction by proximity functions and the compound dual radiation action formalism. Using Monte Carlo methods, LET values of individual alpha particle hits are selected randomly from the LET spectra and corresponding transition rates are taken from the LET-transition rate relationships. This novel microdosimetric formulation of the SVM offers a more realistic description of alpha particle interactions with bronchial target cells, particularly for low exposure levels.

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MECHANISTIC MODELLING OF GENETIC AND EPIGENETIC EVENTS IN RADIATION CARCINOGENESIS

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The serious methodological problems arise on the way of radiation carcinogenesis modelling with incorporation of radiobiological and cancer biology mechanistic data. Here, the new technology based on in silico cell modelling is described. It includes development of biophysical tools for integrative modelling of cellular processes: 3D structures and dynamics of chromosomes in nucleus; DNA damage induction and repair; chromosome aberrations (CA); growth and death of damaged cells; intercellular interactions. We demonstrate that RBE-LET relationship for radiation induced cell neoplastic transformation in vitro (RINT) can be explained in terms of induction of either certain type of CA or two and more DNA dsb clusters in specific chromosomal sites. However, experimental data reveal that RINT is reversible process. This suggests that DNA damage can induce RINT indirectly, via epigenetic process. Modelling study indicates that dynamic chromatin/chromosome reorganisation during M-G1-S transition can contribute to genome replication control. On this basis, the epigenetic mechanism for RINT is suggested. Slow repair of clustered lesions can result in altered chromatin positioning at entry into S-phase and then, in reduced fraction of functioning replicons. This state can be epigenetically inherited and thus be transmitted to the progeny of irradiated cells. In order to proliferate under partially inhibited DNA synthesis those cells may permanently recruit new, genetically not determined, replicons by repositioning new chromatin loops at nuclear matrix. This mechanism may explain some phenomena associated with transformed phenotype: reduction of DNA damage induced G1-arrest, loss of replication origin specification, reversibility of RINT.

MECHANISTIC MODELS OF BONE CANCER INDUCTION BY RADIUM AND PLUTONIUM IN ANIMALS COMPARED TO HUMANS

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Abstract: The dose-effect relationship for bone cancer induced by bone seeking radionuclides such as Ra-226 and Pu-239 exhibits a supra-linear trend. To assess this relationship from a mechanistic viewpoint, we have analysed experimental data of several animal species with a biologically based two-mutation cancer model. This model allows for cells at risk to become malignant in two rate-limiting, mutational steps. In an intermediate stage the growth advantage of premalignant cells is modelled with a clonal expansion process. Joint fits of animal data from several studies indicate similar models for the different animal species. The models exhibit equal linear radiation coefficients (though different for each radionuclide) for both mutation rates at low intakes. The two initially linear mutation rates explain the supra-linear dose response of the bone cancer incidence. This supra-linear response leads to significantly lower risks at low doses than can be estimated from a linear extrapolation to low dose.
To further investigate the implications for human radiation risks, radium dial painter data compiled by Rowland (1994) have been modelled. Application of the two-mutation model to these data leads to similar dose-response relationships for the model parameters as were found for the animal data. The toxicity ratio of Pu-239/Ra-226 derived from animal data can be used in combination with the model for radium in dial painters to estimate the radiation risks of plutonium in humans. In this presentation these risks are compared to epidemiological estimates of the bone cancer risks from plutonium for the Mayak workers.

LUNG CANCER AMONG MAYAK WORKERS

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Workers of the Mayak Production Association in Southern Urals have been exposed to protracted exposures of plutonium and external radiation. Lung cancer mortality was analysed for a sub-cohort of the Mayak workers, which was defined by: male; first employment at Mayak in the period 1948-72; work place in one of the reactors, or in the radiochemical or plutonium production plant; measurement of external dose available; if worker of the radiochemical or plutonium production plant, then assessment of internal lung dose based on urine measurement available; at least two years survival after the first measurement of a-activity in the urine; and smoking information available. The cohort includes 6293 workers. The follow-up was until 31 December 2002. The vital status is known for 97% of the sub-cohort. In total there were 301 lung cancer deaths. The data are equally well described by two different models. The first is a conventional excess relative risk (ERR) model, in which the baseline depends on age attained and smoking status, and the excess relative risk depends on dose and age attained. The second model is a two-step clonal expansion (TSCE) model of carcinogenesis, in which the initiation rate depends on external dose and the clonal expansion rate on smoking status and plutonium dose. The first model results in an estimate of the ERR per lung dose of 7.9 (95% CI: 5.4 - 11.4) Gy-1, the second model in 2.8 (95% CI: 2.0 - 4.0) Gy-1. The reasons for the different results are explored. Implications for assessments of radiation risk are discussed.

CYTOGENETIC METHODS FOR BIODOSIMETRY AND INDIVIDUALIZATION OF RISK AFTER EXPOSURE TO IONIZING RADIATION

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Metaphase chromosome aberration analysis is applied to assess dose received by potentially overexposed people and estimate risk for health effects. Alternatively, molecular cytogenetics in combination with Fluorescence in Situ Hybridization (FISH) and Premature Chromosome Condensation (PCC), which enables analysis in interphase, offer several advantages for biodosimetry. Dose and risk estimates derived using adequate calibration curves, however, are based on the assumption that all individuals respond equally to radiation, but this is not always true. Since increased sensitivity has been highly associated with cancer proneness, there is particular interest in elucidating the mechanisms underlying genetic susceptibility to radiation sensitivity. Towards this end, the efficiency of dynamics that govern cell cycle arrest, DNA repair and apoptosis, as well as the conserved cellular processes that have evolved to facilitate DNA damage recognition using signal transduction pathways to activate cell cycle arrest and preserve genomic integrity, are being investigated. Our recent work on the modulation of radiation effects at the chromosome level using changes in gene expression associated with proteins or factors such as caffeine or amifostine treatment during G2 to M-phase transition of normal and AT cells, showed the importance of cdk1/cyclin-B activity for the conversion of DNA damage into chromosomal damage and provided direct evidence that G2-chekpoint facilitates repair of chromosomal damage. In view of the potential importance of these observations, G2-chromosomal radiosensitivity may offer a basis for the identification or testing of key genetic targets for modulation of radiation effects, and the establishment of a screening method to detect intrinsic radiosensitivity.

COMPUTATIONAL BIOLOGY IN SPACE RADIATION RISK ASSESSMENTS

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Estimating risk from space radiation poses important questions on the radiobiology of protons and heavy ions. We are considering systems biology models to study radiation induced repair foci (RIRF) at low doses, in which less than one-track on average transverses the cell, and the subsequent DNA damage processing and signal transduction events. Computational approaches for describing protein regulatory networks coupled to DNA and oxidative damage sites include systems of differential equations, stochastic equations, and Monte-Carlo simulations. We review recent developments in the mathematical description of protein regulatory networks and possible approaches to radiation effects simulation. These include robustness, which states that regulatory networks maintain their functions against external and internal perturbations due to compensating properties of redundancy and molecular feedback controls, and modularity, which leads to general theorems for considering molecules that interact through a regulatory mechanism without exchange of matter leading to a block diagonal reduction of the connecting pathways. Identifying rate-limiting steps, robustness, and modularity in pathways perturbed by radiation damage are shown to be valid techniques for reducing large molecular systems to realistic computer simulations. Other techniques studied are the use of steady-state analysis, and the introduction of composite molecules or rate-constants to represent small collections of reactants. Applications of these techniques to describe spatial and temporal distributions of RIRF and cell populations following low dose irradiation are described.

DOSE AND DOSE RATE EFFECTIVENESS OF SPACE RADIATION

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Dose and dose rate effectiveness factors (DDERF), in conjunction with other weighting factors, are commonly used to scale atomic bomb survivor data in order to establish limits for occupational radiation exposure, including radiation exposure in space. We use some well-known facts about the microscopic pattern of energy deposition of high energy heavy ions, and about the dose rate dependence of chemical reactions initiated by radiation, to show that DDERF are likely to vary significantly as a function of particle type and energy, cell, tissue, and organ type, and biological end point. As a consequence, the use of a single DDERF to derive radiation limits in space is a compromise that may be required by a lack of further information, and has been found to be useful. However, we argue that validation of this value by conventional methods, e.g., irradiating animal colonies and compiling statistics of cancer mortality, are not feasible within the resources likely to be available.

NUCLEAR FRAGMENTATION AND THE NUMBER OF PARTICLE TRACKS IN TISSUE

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For high energy nuclei, the number of particle tracks per cell is modified by local nuclear reactions that occur, with large fluctuations expected for heavy ion tracks. Cells near the interaction site of a reaction will experience a much higher number of tracks than estimated by the average fluence. Two types of reaction products are possible and occur in coincidence; projectile fragments, which generally have smaller charge and similar velocity to that of the projectile, and target fragments, which are produced from the fragmentation of the nuclei of water atoms or other cellular constituents with low velocity. In order to understand the role of fragmentation in biological damage we have developed a new model of human tissue irradiated by heavy ions. The tissue is represented as a cell matrix based on microscopy and experimental data. A box of the tissue is modeled with periodic boundary conditions imposed, which extrapolates the technique to macroscopic volumes of tissue. The radiation applied to the cells has the parameters of space radiation, particularly galactic cosmic rays (GCR). The cross sections for projectile and target fragmentation products are taken from the quantum multiple scattering fragmentation (QMSFRG) code previously developed at NASA Johnson Space Center. We report the statistics of fragmentation pathways occurring in a cell monolayer, as well as a small volume of 10x10x10 cells. We discuss approaches to extend the model to describe spatial distributions of inactivated or other cell damage types, as well as highly organized tissues of multiple cell types.

MICRODOSIMETRIC ANALYSIS OF RBE DOSE DEPENDENCE FOR HIGH LET RADIATION

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For radiation therapy using high LET particles the biological effects are strongly affected by the heterogeneity of the specific energy (z) distribution delivered to tumor cells. A novel microdosimetry analysis method, which is able to estimate this distribution directly based on the two-dimensional spatial information of cell morphology and nuclide distribution from microautoradiography, has been developed and verified by Monte Carlo simulation. In this paper we applied this method to high resolution quantitative autoradiography (HRQAR) specimens in Boron Neutron Capture Therapy (BNCT), and hypothesized a biophysical model based on specific energy for survival analysis.
The specific energy (z) distributions to cell nuclei were calculated for both glioblastoma multiforme (GBM) and normal brain tissue specimens. The mean values of the specific energy were found to be consistent with the MIRD (medical internal radiation dose) results, suggesting a microscopically uniform distribution of the boron compound, boronophenylalanine-fructose. However, the wide variation of the specific energy distribution indicates a significant heterogeneity of biological effect. By combining this microdosimetric analysis with measured cell survival data, a cell survival curve with decreasing steepness at high doses is predicted, which fits a linear-quadratic model with a negative quadratic term. As a result, the model predicts a reduction in the RBE from 3-4 at low dose to less than 2 at 20 Gy. This finding, different from the current theoretical models, may have general implications for high LET radiation.

MICRODOSIMETRIC MODELLING OF RESPONSE OF THERMOLUMINESCENCE DETECTORS TO LOW- AND HIGH-LET IONISING RADIATION

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Thermoluminescence (TL) dosimetry relies on evaluating the dose absorbed in the TL detector by measuring the light output by the detector. However, the TL light emission per unit dose of ionising radiation absorbed in the detector is known to depend on the energy and quality (ionisation density) of this radiation. Measurements of the response of TLD after -ray doses high enough to observe signal saturation provide input to microdosimetric models which relate this -ray response with the energy response after low doses of photons gamma-rays and low-energy X-rays) and after high-LET irradiation. This paper describes the microdosimetric models, which has been applied to calculate dose and energy (LET) response of TL detectors. The measured dose response after 60Co -rays irradiations over the range 1 - 5000 Gy for LiF:Mg,Ti, LiF:Mg,Cu,P, CaSO4:Dy and Al2O3:C detectors were applied to predict the thermoluminescence dose response and relative TL efficiency, , after irradiations with X-rays, -rays, -electrons and Heavy Charged Particles (HCP). Microdosimetric distributions in nanometer site targets for photons and -rays were calculated using TRION MC track structure code, for HCP using the analytical model of Xapsos with the modified transport of secondary electrons. The calculated values of compare favourable with the broad spectrum of experimental data, including ICHIBAN experiments with HCP. The microdosimetry may offer a valuable contribution to solid state dosimetry to mechanistic explanations of physical phenomena in different thermoluminescence detectors.

A SOLID STATE MICRODOSIMETER BASED ON A MONOLITHIC SILICON TELESCOPE

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Silicon devices can provide micrometric sensitive zones which can be exploited to measure microscopic distributions of energy deposition. However, the realization of a solid state microdosimeter based on a silicon detector may be limited by: (i) the minimum detectable energy which affected by the electronic noise; (ii) radiation hardness; (iii) the geometry of the sensitive volume, which is usually parallelepiped (and not spherical like in the conventional microdosimeters, such as the tissue equivalent proportional counters); (iv) the field-funnelling effect (due to a local distortion of the electric field in the depletion layer, induced by high-LET particles, leading to the collection of electron-hole pairs produced in the non-depleted zone); (v) the non tissue-equivalence of silicon.
A monolithic silicon telescope, consisting of a E and an E stage-detector (about 2 m and 500 m thick, respectively), was coupled to a polyethylene converter and irradiated with monoenergetic neutrons at the INFN-Laboratori Nazionali di Legnaro (Legnaro, Italy). The experimental spectra were compared with Monte Carlo simulations and with the results of an analytical model for the detector response. The field-funnelling effect appears to be negligible, while the effects of the sensitive volume geometry affects the profile of the energy distributions, especially in the high-energy part of the spectra. The possibility of correcting analytically these geometry effects using the signals generated in the E-stage will be discussed. The preliminary results of an inter-comparison with microdosimetric spectra measured with a TEPC will be also presented.

NANODOSIMETRY, THE METROLOGICAL TOOL FOR CONNECTING RADIATION PHYSICS WITH RADIATION BIOLOGY

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It is generally accepted that the early damage to genes or cells by ionizing radiation starts with the early damage to segments of the DNA, at least, to the greater part. This damage is the result of the spatial distribution of inelastic interactions of single ionizing particles within the DNA or in its neighbourhood and is, in consequence, determined by the stochastics of particle interactions in volumes, a few nanometre in size. Due to the latter fact radiation damage strongly depends on radiation quality and cannot be described satisfactorily in detail by macroscopic quantities like absorbed dose or linear energy transfer (LET). It can, however, be described approximately by the probability distribution of ionization cluster-size formation in nanometric target volumes of liquid water (nanodosimetry).
One aim of nanodosimetry is, therefore, to measure the radiation induced frequency distribution of ionization cluster-size formation in liquid water, as a substitute to sub-cellular material, in volumes which are comparable in size with those of the most probable radio-sensitive volumes of biological systems. After a short description of the main aspects of cluster-size formation by ionizing particles, an overview is given about the measuring principles applied in present-day nanodosimetric measurements. Afterwards, physical principles are discussed which can be used to convert ionization cluster-size distributions measured in gases into those caused by ionizing radiation in liquid water. In a final section, the probability distribution of ionization cluster-size formation in liquid water is discussed from the point of view of damage formation to segments of the DNA.

ION-COUNTING NANODOSIMETER WITH PARTICLE TRACKING CAPABILITIES

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In recent years, we have developed an ion counting nanodosimeter capable of measuring the distribution of radiation-induced ions in a millimetric, wall-less sensitive volume in a low-pressure gas. The sensitive volume models an equivalent nanometric volume of DNA. At Loma Linda University Medical Center (LLUMC), this device has been equipped with a silicon microstrip telescope that tracks the primary particles, allowing correlation of nanodosimetric data with particle position relative to the sensitive volume. Here we report on the design and performance of this tracking nanodosimeter, tested with a broad 250 MeV proton beam. We demonstrate that particle coordinate information in the silicon tracker combined with nanodosimetric data can map the ionization pattern of track segments in three dimensions within a few hundred nanometer-equivalent volume and with a resolution of about 5 tissue-equivalent nanometers. The precision tracking capability also enabled us to perform measurements aimed at verification of the wall-less sensitive volume dimensions, for which only simulated data were available. We have seen that the tracking nanodosimetry data and Monte Carlo simulation results agreed well, thus allowing application of this technique to experimental track-structure studies of charged particles.

3D MICRODOSIMETRY FOR MICROBEAM RADIATION THERAPY (MRT)

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Microbeam Radiation Therapy (MRT) uses highly collimated parallel microbeams of very high dose rates (20 Kgy/sec) generated by 3rd generation synchrotron sources, like on ID17, the medical beamline at the ESRF in France. Such ~25 micron wide beams separated by center-to-center (c-t-c) distances in the range of 100 - 400 microns are extremely well tolerated by the normal tissue using entrance doses of roughly 600 Gy. This phenomena was particularly studied in the developing brain of mice rats and piglets giving credit to use this promising technique for brain cancer treatment in children, since other kinds of radiotherapy would be excessively toxic to the developing normal brain. MRT uses extraordinarily high doses of X-rays but provides unusual resistance to radioneurotoxicity, presumably from the migration of endothelial cells from "valleys" into "peaks", i.e., into directly irradiated microslices of tissues. We present an irradiation geometry which results in a tolerable valley dose for the normal tissue and a decreased peak-to-valley dose ratio (PVDR) in the tumour area applying an interlaced cross-firing technique by orthogonally crossing two arrays of parallel, nonintersecting, mutually interspersed microbeams that produces tumouricidal doses with small PVDRs where the arrays meet and tolerable radiation doses to normal tissues between the microbeams proximal and distal to the tumour in the paths of the arrays. A 3D microdosimetry with spatial resolution in the range of microns using Gafchromic films and a microdensitometer will be presented as well as feasibility studies on the improvement to choose different PVDRs for the tumour zone and the normal tissue using such interlaced crossfire techniques.

HAS MICRODOSIMETRY CONTRIBUTED TO PROGRESS IN RADIATION MEDICINE?

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1. Microdosimetry and radiotherapy
Microdosimetry has frequently been used to predict RBEs between different clinical therapy beams, to establish treatment dose for the new modality. In times past, this was more for estimating RBEs for neutrons and charged particles, vs. photons, but it is now more often used for estimating RBEs for different low-energy photon brachytherapy isotopic sources, as well as miniature x-ray generators. It is important to note that RBEs calculated from single-event microdosimetric data refer to low doses of the radiation in question, and not to clinically relevant doses. Clinically relevant RBEs, which are much lower, can and should be calculated and used.
2. Microdosimetry and radiology
A current application here relates to the use of low-energy photons for mammography. There has been an ongoing debate as to whether the low-energy photons used in mammography are more biologically effective (and if so by how much) than higher energy photons (e.g. those relevant at Hiroshima and Nagasaki, from which risk estimates are generated). Microdosimetry provides an excellent tool for understanding this situation.
3. Microdosimetry and low-dose risk estimation
More generally, there has been much debate about whether doses from radiological examinations can themselves cause cancer, and microdosimetry again provides a useful tool for examining this issue. The so-called microdosimetric argument is central to the debate about the risks of low doses of radiation. Essentially the argument goes:
A. There is direct epidemiological evidence that an organ dose of ~10 mGy of diagnostic x rays is associated with an increase in cancer risk.
B. At an organ dose of 10 mGy of diagnostic x rays, most irradiated cell nuclei will be traversed by one, or at most a few, physically-distant electron tracks.
C. If the dose is decreased, say by a factor of 10 to 1 mGy, this will simply result in proportionately fewer electron tracks and proportionately fewer hit cells. Thus those proportionately fewer cells that are hit at the lower dose, a) will be subject to essentially the same types of electron damage, and b) will be subject to the same radiobiological processes, as would occur at 10 mGy.
D. Thus, decreasing the number of damaged cells by a factor of 10 would be expected to decrease the biological response by the same factor of 10, i.e. response would decrease linearly with decreasing dose. One could not expect qualitatively different biological processes to be active at, say, 1 mGy that were not active at 10 mGy, or vice-versa.
The microdosimetric argument suggests that the risk of most radiation-induced endpoints will decrease linearly, without a threshold, from ~10 mGy down to arbitrarily low doses. The argument, of course, contains a number of assumptions, particularly in regard to autonomous responses of individual cells. These will be discussed critically.

THE RBE ISSUES IN ION-BEAM THERAPY: SOME CONCLUSIONS OF A JOINT ICRU/IAEA WORKING GROUP RELATIVE TO QUANTITIES AND UNITS

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Absorbed dose is a physical, rigorously defined quantity. It is a fundamental quantity in radiation therapy, protection and radiobiology. However absorbed dose alone does not allow one to predict the biological effects because such effects vary with dose per fraction, dose rate, radiation quality, irradiation condition, the biological system involved and the type and magnitude of the effects.

Therefore, in radiation therapy, for comparing and/or combining irradiations performed under different conditions, weighting factors (or functions), W, have to be introduced. This implies the selection of reference irradiation conditions. Today, there is a general consensus among the radiation-therapy community to select an irradiation performed, with photons, at 2 Gy per fraction, 5 fractions a week as the reference.

The product of absorbed dose D by the weighting factor W is the "isoeffective dose", D(IsoE), i.e., the dose that delivered under the reference conditions (photons, 2 Gy/fr, 5 fr/w) would produce the same clinical effect as the actual treatment. D and D(IsoE) are both expressed in Gy. Specification of the isoeffective dose implies the description of the clinical effects evaluated, the approach used and the numerical values of the involved quantities.

The weighting factor applied to the absorbed dose to derive the isoeffective dose is the "isoeffective-dose weighting factor" W(IsoE). It is a global factor that combines the influence of different factors such as dose per fraction (L-Q, a/ß model), radiation quality (LET, RBE), and irradiation conditions. These factors are not independent (e.g., the a/ß values for photons and carbon ions are different, etc).

In external photon-beam therapy, W(IsoE) is currently evaluated for different doses per fraction and there is a general agreement on the numerical values of the a/ß ratios for early and late clinical effects (10 and 3 Gy, respectively). In brachytherapy, in addition, the kinetics of cell repair has to be taken into account in high dose-rate (HDR) and pulsed dose-rate (PDR) brachytherapy).

To apply carbon-ion therapy under efficient and safe conditions, in addition to the factors mentioned above, the RBE has to be taken into account when selecting W(IsoE). The RBE of ions, relative to photons, is not a fixed value but varies significantly with the type and energy of the ions, dose per fraction and overall time, position (depth) in the beam and type of clinical effects (early or late). Dose weighting for the RBE, and selection of the global weighting factor W(IsoE) raise complex practical issues in ion-beam therapy. No general agreement has been reached so far on the approach to be recommended and the numerical values to be applied.

Finally, selection of W(IsoE), that determines the prescribed dose, rests on the decision and judgment of the radiation oncologist in charge of the patient or, alternatively, of the team deciding on the treatment protocol in the case of a collaborative study).

A SIMPLE TRACK STRUCTURE MODEL OF ION BEAM RADIOTHERAPY

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We present a simple radiotherapy ion beam calculation based on the cellular track structure model, using in vitro cell survival parameters fitted from recent experimental data. The depth distribution of cell survival is directly calculated over the range of the stopping ion, as a sequence of track-segments, in the continuous slowing-down approximation. The calculation represents a single-fraction ion exposure corresponding to a 2 Gy fraction of megavolt X-rays and exploits concepts used in clinical radiotherapy, such as entrance, or "skin" dose. An interpretation of the "clinical RBE" concept is suggested. We propose that the complex calculations of "biologically equivalent dose" distributions over the target volume be replaced by a direct comparison between cell survival over the tumour volume after exposure to radiotherapy beams of different modalities. Calculations are performed for light ions (up to 12C) to discuss the possible advantages of using ions lighter than carbon in radiotherapy.

TECHNIQUES FOR RADIATION MEASUREMENTS: DOSIMETRY AND MICRODOSIMETRY

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This 'Refresher Course' will explore the various radiation measurement techniques that have been developed during more than four decades of experimental microdosimetry. Through an examination of some of the quantities used in radiation metrology and dosimetry the natural link with microdosimetric techniques will be shown and the particular benefits of using microdosimetric methods for dosimetry illustrated.

At the centre of all microdsimetric investigations is the question of radiation quality and how it can be specified in terms of the distribution of energy deposition arising from the interaction of a radiation field with a particular target site. Over the years our understanding of what is the best representation of a target has evolved along with the biological information concerning radiation effects. Rather than these studies leading to an unequivocal specification of a site size to describe radiation quality, we have arrived at the position where it seems that radiation quality needs to be described by energy deposition on the nanometer, micrometer and millimeter size scales. With this in mind, the presentation will discuss the various techniques that have been developed to measure radiation energy deposition over the three orders of magnitude of site size required. Inevitably, much of the discussion will concern the use of tissue equivalent proportional counters and variants of this device, but an effort will be made to cover other technologies that have been studied or are under development for their potential in experimental microdosimetry.

A SYSTEMS BIOLOGY APPROACH TO MULTICELLULAR AND MULTI-GENERATIONAL RADIATION RESPONSES

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Recent studies have highlighted crosstalk between irradiated cells and non-irradiated bystander cells and have uncovered high-frequency phenotypes of genomic instability in the progeny of irradiated cells. Rather than viewing these cell responses as additional risks of radiation, one may consider the problem from a systems biology viewpoint. Key differences between systems biology and current reductionist paradigms are that systems biology places emphasis on networks versus components, distributed versus centralized effort, and redundancy versus uniqueness. Systems biology attempts to organize multiscale data obtained following environmental perturbations and use that data to build a descriptive and mechanistic model of the biological phenomena. Top-down analysis of the radiation response of any organism, much less humans, is beyond present capabilities because neither the tools nor detailed, global data are available. Yet, it is feasible to use systems biology concepts to place radiation-induced bystander effect, adaptive response and genomic instability into the context of an irradiated system (i.e. tissue). Radiation-induced bystander effects are a type of multicellular responses to radiation, while adaptive response and multi-generational radiation-induced genomic instability may result from persistent network perturbations following radiation exposures. A model of radiation response based on the systems biology principles of network interconnectivity, redundancy and spatial organization within the higher order structure of tissues and organisms could improve current models of the risks from ionizing radiation exposure.

PREDICTION OF BIOLOGICAL RESPONSES TO INCORPORATED RADIOACTIVITY

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Prediction of risks and therapeutic outcome in nuclear medicine largely rely on calculation of the absorbed dose. Absorbed dose specification is complex due to the wide variety of radiations emitted, nonuniform activity distribution, biokinetics, etc. Conventional organ absorbed dose estimates assumed that radioactivity is distributed uniformly throughout the organ. However, there have been dramatic improvements in dosimetry models that reflect the substructure of organs as well as tissue elements within them. These models rely on improved nuclear medicine imaging capabilities that facilitate determination of activity within voxels that represent tissue elements of about 0.2 - 1 cm3. However, even these improved approaches assume that all cells within the tissue element receive the same dose. The tissue element may be comprised of a variety of cells having different radiosensitivities and different incorporated radioactivity. Furthermore, the extent to which nonuniform distributions of radioactivity within a small tissue element impact the absorbed dose distribution is strongly dependent on the number, type, and energy of the radiations emitted by the radionuclide. It is also necessary to know whether the dose to a given cell arises from radioactive decays within itself (self-dose) or decays in surrounding cells (cross-dose). Cellular response to self-dose can be considerably different than its response to cross-dose from the same radiopharmaceutical. Bystander effects can also play a role in the response. Evidence shows that even under conditions of "uniform" distribution of radioactivity, a combination of voxel dosimetry and dosimetry at the cellular and multicellular levels can be required to predict resp

HEALTH RISKS OF LOW PHOTON ENERGY IMAGING

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Dose-response relationships for the endpoint of neoplastic transformation in vitro as a consequence of irradiation by low doses of low energy photons will be discussed in terms of their relevance to both mechanisms of radiation response at low doses and cancer risks associated with such exposures. An emphasis will be placed on mammography and breast cancer risk.

POSTER

PRESENTATIONS

A 1

IONIZATION RANGES OF PROTONS IN THE ENERGY RANGE 1 KEV-100 KEV

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If tissue is irradiated by neutrons or other heavier particles, protons are set in motion as recoils in a large amount. The knowledge of basic physical data describing the interaction of protons with matter is therefore of great importance. One of the basic physical data for this purpose is the proton range which is necessary for the estimate of the distance of energy depositions.
To our knowledge there are no experimental data for the range of protons in water, despite the fact that tissues are for the greater part made up of water. Therefore, the so-called ionization ranges were determined experimentally for protons at energies between 1 keV and 100 keV in water vapour for ionization fractions of 90%, 95% and 99%. Here, the ionization range is defined as that thickness of a material which is penetrated by a particle in its initial direction and causes a specified fraction of the ionization produced upon complete slow down.
Using these experimental ranges and the detour factor, the continuous slowing-down ranges were calculated and compared with literature values. The comparison shows a satisfactory agreement in the above energy range. Furthermore, the energy dependences of the proton range curves for different ionization fractions were compared and stopping power was derived from the range curves.

A 2

GEANT4 SIMULATION OF VERY LOW ENERGY INTERACTIONS IN LIQUID WATER

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A set of models for Monte Carlo simulation of electron, proton and alpha electromagnetic interactions in liquid water down to ~7.5 eV is developed in the Geant4 toolkit framework for the Geant4 DNA project. The following physics processes are implemented: elastic scattering, excitation, ionization, and charge transfer. These interactions are of particular importance to biomedical applications due to the abundance of this substance in biological tissues. In particular, an accurate tracking of electrons is essential as secondary electrons of proton and alpha interactions are responsible for most of the energy deposited. Elastic scattering is based on the semi-empirical approach proposed by Brenner-Zaider (below 200 eV), and on the Rutherford formula including a screening correction term proposed by Emfietzoglou (above 200 eV). Electron inelastic interactions are described using the theory of Born taken from Emfietzoglou et al. Excitation by protons is based on the Miller and Green model, while ionization uses also the Born theory taken from Dingfelder et al. Both electron and proton models take into account the A1B1, B1A1, Ryd A+B, Ryd C+D, and diffuse bands for the excitation process, and 1b1, 3a1, 1b2, 2a1, and the oxygen K-core shells for the ionization one. Hydrogen and alpha excitation and ionisation are modelled from the corresponding proton interactions taking into account the projectile effective charge. Proton charge transfer, alpha charge transfer and neutral hydrogen stripping are also described by semi-empirical formulas taken from Dingfelder et al.

A 3

RADIATION QUALITY OF TRITIUM

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Tritium occurs from both natural and manufactured processes. Nuclear facilities can release tritium to the environment during normal operation. In the environment, tritium can exist in the form of tritiated water (HTO) and in an organic form known as organically-bound tritium (OBT). Although the concentrations of environmental OBT are relatively low, there is concern that current risk factors may underestimate the risk from OBT. Because tritium poses internal hazard at cellular levels, microdosimetric techniques provide suitable tools for the study of radiation quality of tritium. In this study, microdosimetric simulations are performed for tritium uniformly distributed in a medium, and for tritium bound to biologically critical sites in dimensions from 10 nm to 2 ?m. Results of local energy density are different for these two cases in microscopic regions. Based on the spatial distribution of energy deposition, dose mean lineal energies are calculated for tritium in forms of HTO and OBT. The dose mean lineal energies of OBT are consistently about a factor of 2 higher than those of HTO in wide target dimensions of biological interest. The results are consistent with radiobiological findings that the relative biological effectiveness (RBE) of tritium when bound to nuclear bases is about twice effective as that of HTO.

A 4

PROXIMITY FUNCTIONS FOR ELECTRONS FROM 100 EV TO 10 MEV

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The objective of this study is to provide a set of proximity functions for electrons up to 10 MeV. It is an extension of a previously published article for electrons up to 10 keV. The proximity function is a spatial auto-correlation function of the microdistribution of energy imparted within particle tracks. It characterizes radiation quality by specifying the distribution of distances between energy transfers in the particle track. The concept has been variously applied for the analysis of radiobiological studies. In radiation protection, the important microdosimetric parameter, the dose mean lineal energy, can be derived from proximity functions for any specified microscopic site. It is, therefore, desirable to obtain proximity functions for different types of radiation. Although Monte-Carlo codes are well developed for the simulation of charged particle tracks, a systematical effort has not yet been made to generate complete sets of proximity functions for the most important radiations. As a step toward establishing the necessary data set, the proximity functions for electrons up to 10 MeV in water are computed. Results of differential proximity functions are given graphically. Detailed numerical results for electrons of 65 different energies are available electronically upon request from the corresponding author.
The proximity functions of monoenergetic electrons are essential and can be used to derive the functions of other radiation qualities. Examples are given to construct the proximity functions of tritium and 250kV x-rays.

A 5

THE NEW ANALYTICAL MODEL FOR CALCULATION OF MICRODOSIMETRIC DISTRIBUTIONS FOR HEAVY IONS

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Ionizing radiations are known to induce a wide variety of biological effects of direct relevance on humans, including cell killing or mutation. As the space program enters an era of extended manner space operations the protection of astronauts from galactic radiation becomes an important issue. The interaction of high-energy heavy ions originating in deep space with body tissues results in energy deposition. Energy deposition distributions in nanometer and micrometer size targets (microdosimetric spectra) are considered to be of relevance to explain these radiation actions that could also be similar to these present in physical detectors. The distributions can be effectively measured with the help of tissue-equivalent, low pressure proportional counters, TEPC, or calculated using Monte Carlo or analytical methods. The analytical approach of Olko and Booz was applied in the last decade to calculate the ionization distribution in water targets for ions energy range from up to 10 MeV/amu and Z=1 to Z=8 (Olko 2003). This model attempted to parameterized the results of Monte Carlo calculations of microdosimetric distributions using track structure code MOCA-14. However, the MOCA-14 has the limitations to 10 MeV/amu ionizing particle energy and can not be used for calculation of microdosimetric distributions of high energy heavy ions. The aim of this work was to adapt Xapsos (1994) analytical model for modeling of interaction of heavy ions with energy range up to hundreds MeV/amu. The convenient and versatile model is based on the observation that the energy loss straggling approximates a lognormal distribution with the parameters given in terms of relative variance of the random variables involved in energy deposition process. In this work, the few improvements related to development of ? electrons part of model, including the model of electron transport (Brahme 2000) has been tested and implied in the Xapsos approach in order to improve the simulation effectiveness specially by the HZE ions. The new, improved and adapted Xapsos model has been compared with results of earlier Olko and Booz simulations as also with MC simulations (Nikjoo 2002) of wall-less proportional counters response functions. The calculated responses of TEPC on various types of heavy ion radiation beams (Z=8 and Z=18) has been compared showing the good agreement. The Xapsos model has been next applied for calculation of relative TL efficiency of MCP-N (LiF:Mg,Cu,P) TL detectors for heavy ions. The microdosimetric spectra for ions used at the Chiba accelerator has been calculated, the relative efficiency obtained by applying of Kellerer one - hit detector model. Results were compared with measurements (Bilski, Horwacik 2004) .The calculated and measured efficiencies for Z=2 up to Z=26 and energy range form 150MeV/amu up to 500MeV/amu ions agrees within 10-15%. Further studies of secondary electron spectra are needed as also the work of optimalisation of the algorithm must be done.

A 6

PREDICTION OF DOSE RESPONSE FOR RADIATION INDUCED EXCHANGE ABERRATIONS TAKING CELL CYCLE DELAYS INTO ACCOUNT

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Chromosomal aberrations (CA) are regarded as the most sensitive biological indicator of genetic alterations. The aberration frequency is routinely determined in human lymphocytes in first metaphase at 48 h postirradiation. Yet, interpretation of data is complicated due to differential, damage-dependent radiation-induced delays of cells.

To investigate the effect of mitotic delay on CA frequency in mitosis, isolated human lymphocytes were irradiated with X-rays and CA detectable with Giemsa staining were measured in the first cycle mitoses each 3 h between 48 and 84 h postirradiation. Ratios of first/second/third cycle metaphases were determined. Analysis showed only a slight increase in the aberration yield with sampling time.

The lymphocyte transition through cell cycle in control and after X-irradiation was simulated by Monte Carlo technique. The mitotic delay was proposed to result from unrepaired DNA dsb. The delay time and frequencies of CA seen in first metaphase at any time were calculated. The CA formation model took into account structural organisation of interphase chromosomes in lymphocyte nucleus, dsb induction and rejoining/misrejoining. The predicted ratios of first/second/third cycle metaphases were in good agreement with the experimental data for both control and irradiated samples. The calculated frequency of CA, like the experimental one, was nearly independent of sampling time. This independence is predicted to be due to heterogeneity of lymphocyte population: several sub-populations are supposed to exist with different cycle duration and radiation-induced delay time. Hence cells reach first mitosis at wide time range which masks the later appearance of heavily damaged cells in mitosis.

A 7

A COMPARATIVE STUDY OF DIELECTRIC RESPONSE FUNCTION MODELS FOR LIQUID WATER

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The dielectric response function (DRF) is the important material property for calculating inelastic scattering cross sections in condensed media. Important transport parameters such as the energy loss spectrum in a single interaction, the mean free path, the stopping power, and the straggling parameter may be directly obtained by suitable integrals over this function. Furthermore, it accounts for polarization and screening effects due to the long-range Coulomb interactions in the condensed phase which are absent in the gas phase (at normal pressures). In this work, we compare various methodologies that aim at an analytic representation of the DRF of liquid water over the complete spectrum on the energy-momentum plane. The use of optical data is a common feature to all methodologies providing an empirical ground for modeling the energy dependence of the valence-loss spectrum where many-body (and phase) effects are expected to be most prevalent. In recent years, by means of inelastic X-ray scattering (IXS) spectroscopy the Bethe surface of liquid water has been experimentally determined. This provides, for the first time, the opportunity for testing the accuracy of the dispersion models adopted so far for describing the momentum dependence of the DRF. We have recently developed a self consistent parametrization of the full IXS spectrum of liquid water along the lines of the extended Drude algorithm. It is shown that notable discrepancies exist between the various models, both at the optical and Bethe ridge limit. The implication to the calculation of electron transport characteristics is discussed.

A 9

W- VALUES AND STOPPING POWERS FOR ELECTRONS IN METHANE BASED TISSUE EQUIVALENT MATERIALS FROM 10 TO 10000 EV

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Tissue equivalent (TE) gases are commonly used to fill radiation detectors in biological and medical dosimetric applications. They absorb energy as the soft human tissue giving a direct measurement of the equivalent dose. Since the energy transfer to the medium can be described in terms of secondary electron interactions with their atomic and molecular constituents, we present in this work a complete set of molecular parameters (electron scattering cross sections, electron energy loss spectra, W-values and electron stopping powers) that can be useful to study the energy deposition of radiation in these materials from 10 to 10000 eV.

Total electron scattering cross sections for a methane based TE gas have been measured in a transmission beam experiment [1] for energies ranging from 10 to 10000 eV . Experimental errors were of the order of 3%. Ionisation cross sections were determined in this range, with uncertainties of about 7%, by simultaneous measurements of ion and electron currents in the scattering chamber. The electron energy loss spectra were measured from the scattered electrons by means of a hemispherical electrostatic spectrometer with an energy resolution of 0.5 eV.

Differential and integral electron scattering cross sections have been calculated for this target by using an optical potential method in the framework of the independent atom model with relativistic, local velocity and screening corrections [2-3].

By combining these theoretical and experimental data, W-values and stopping powers (STP) for electrons in methane based TE gases have been determined. The present results show some discrepancies with the STP values available in the literature [4] that will be discussed in our contribution.

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A 10

RADIATION DAMAGE IN CELLULAR ENVIRONMENT: THE CASE OF WATER

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The high intensity and broad spectral range when combined with other properties such as high degree of polarization and collimation makes synchrotron radiation a powerful tool for basic and applied research [1]. It has been widely used for studying photo-induced physics and chemistry in research areas such as physics, chemistry, biology and medicine.

Biological damage induced by radiation may be attributed to the energy of the ionising radiation being channelled into secondary electron emission. The secondary electrons subsequently collide with the surrounding molecules that can lead to strand breaks in the genetic DNA material [2].

In order to quantify the risk from radiation damage and modelling the effect of radiation on cellular material, it requires a detailed understanding of the underlying interactions between the primary radiation (e.g. UV photons) and the biomolecules (e.g., DNA). This may, in turn, provide information about the molecular pathways that lead from initial deposition of radiative energy to the formation of irreversible biomaterial damage.

Water is also the key component of all living organisms, playing an important role in the cellular environment as a universal solvent [3]. Our understanding of radiation damage within cells, and thence mutagenesis, depends upon the modelling of tracks through the cell, in turn depending upon our knowledge of collisional cross sections with water and the nature of its electronic states and their dissociative pathways leading to production of OH radicals [4].

We, therefore, are focusing our present studies on the VUV radiation on water, providing results on the molecular system's spectroscopy. Knowledge of the photo-absorption processes is also extremely necessary if we are to evaluate the role of these molecular systems in physiological environments.

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A 11

MONTE CARLO MODELING OF ENERGY DEPOSITION IN TRABECULAR BONE

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Myeloproliferative disorders such as leukemia can result from the exposure of ionizing radiation to the bone marrow housed between strands of trabecular bone. For this reason, accuracy in determining the predicted dose to trabecular bone, as well as the marrow it houses, is of vital importance in the field of microdosimetry. Since regional dimensions are on the order of several hundred microns, and being of an irregular shape, experimental methods of dose determination are limited. Instead, computational simulations of radiation transport through a representative model are being performed. For our applications, we are using the general purpose Monte Carlo radiation transport code PENELOPE. The extent to which a simulation represents the actual transport of radiation through the medium relies on two vital aspects: the validity of the transport code and the validity of the geometric representation of the media. While the accuracy of PENELOPE has been proven in many published benchmark studies, the emphasis of this study is placed on creating a valid geometry representative of the actual trabecular region. Currently under development is a program designed to create a PENELOPE-compatible model of this complex target region. Using the same quadric-based constructive geometry subroutines as are used by the latest (beta) version of PENELOPE, this program is designed to create a geometry the resembles the various physical attributes of actual trabecular bone. The resultant geometry serves as the basis for further mircrodosimetric studies in this important region. This work is supported in part by NASA Grant NNJ04HF39G and DOE Grant DE-FG02-01ER63233.

A 12

LOW- AND HIGH LET DOSE COMPONENTS OF PRIMARY AND SECONDARY PARTICLES IN THE THERAPEUTIC LIGHT ION BEAM.

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Clinical application of light ion beams requires correct understanding of the complex processes of ion interaction with matter and the development of accurate transport methods. Especially knowledge of the fluence and LET distributions of primary and secondary particles are necessary for accurate evaluation of the beam quality, RBE of the therapeutic beam as well as for the accurate dosimetry in the ion beams. The track lengths differential in energy of the primary and secondary particles were calculated in the tissue equivalent materials irradiated by ion beams such as 1H, 4He, 7Li, 12C, 20Ne and 28Si using the Monte Carlo code SHIELD-HIT. The SHIELD-HIT code has been benchmarked extensively, and its results were found to be in good agreement with the available experimental data for various phenomena studied. A careful analysis of the low- and high LET particle distributions and the corresponding dose components evaluated at different depths in a tissue phantom are presented.
The Monte Carlo results are compared with the experimental LET distributions for carbon and neon beams from the HIMAC facility measured by the multi-wire parallel-plate proportional counter.
These studies are of high importance for the precise calculations of the dose delivered to tissue and correct evaluation of the relative biological efficiency in light ion therapy.

A 13

EXPERIMENTAL FRAGMENTATION STUDIES WITH 12C THERAPY BEAMS

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High energy carbon ions penetrating matter undergo nuclear fragmentation. For heavy ion therapy this effect is of particular importance as it affects the depth-dose profile and results in a complex radiation field. The primary particle beam is attenuated exponentially with increasing depth and the build-up of lighter fragments gives rise to a dose tail behind the Bragg peak.
Using 200 MeV/u and 400 MeV/u 12C beams delivered by the heavy ion synchrotron SIS-18 we investigated the fragmentation characteristics of these beams in a water absorber of variable thickness. The data include depth-dose profiles (Bragg curves), attenuation of the primary ions and build-up of fragments as a function of depth. For the 12C beam attenuation measurements a telescope detector positioned close to the target exit provided energy loss and total energy information. It was found that approximately 60% of the 200 MeV/u and 30% of the 400 MeV/u primary 12C ions reached the Bragg peak. The absolute Bragg peak positions in water for the two energies were determined to 8.65±0.05 g/cm2 and 27.47±0.05 g/cm2 in the preliminary analysis. In addition, angular distributions for charged fragments were measured with the 400 MeV/u beam at various water depths. Particles were identified by coincident recording of time-of-flight and energy loss signals. The measurements were performed at angles from 1º to 10º in steps of 0.5º to 2º. At angles larger than 10º only H and He were detected. By integration of the angular distributions fragment yields were obtained.

A 14

HYDRATED THYMINE CLUSTERS IN THE SUPERSONIC GAS JET

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Fragmentation of hydrated thymine clusters in the gas phase induced by laser pulse at 266 nm was studied by means of time-of-flight mass spectrometry. The experimental system consists of vacuum chambers, a nozzle for cluster production, a Q-switch Nd:YAG laser and a typical time-of-flight mass spectrometer. The water vapor and thymine one were simultaneously injected through the nozzle into the high vacuum region, and then hydrated thymine clusters were formed by supersonic expansion in the gas jet. The laser pulse was focused in the gas jet, and the range of laser intensity was from 106 to 1010 W/cm2. In the condition of low laser intensity, the peaks corresponding to hydrated thymine cluster ((C5H6N2O2)m(H2O)n), thymine cluster ((C5H6N2O2)n) and thymine monomer (C5H6N2O2) were obtained clearly. In the laser intensity region of 108-109 W/cm2, a fragment molecule (C4H5NO) released from thymine was mainly obtained. This fact means C-N bond breaks in a ring structure of thymine.

A 15

THE COMPARISON OF CALCULATED AND EXPERIMENTAL MICRODOSIMETRIC DISTRIBUTIONS FOR CARBON IONS

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Growing interest in application of carbon ions in tumor therapy requires further investigation of their deposited energy distributions. The aim of this work is to present microdosimetric characteristics of carbon ions with energies in the range of 100 - 1000 MeV/n obtained by theoretical calculations and to analyze them with respect to experimental data obtained by track etched detectors based on polyallyldiglycolcarbonate.
Track structures obtained using Monte Carlo code TRIOL (Bigildeev and Michalik, 1996) are used as an input data for calculations of energy distributions. The calculations of frequency y*f(y) and dose y*d(y) distributions are performed using own developed programs. The theoretical results will be compared and discussed with respect to experimental data obtained on the base of detectors irradiation at NSRL, Brookhaven, USA; HIMAC - NIRS, Chiba, Japan; and LHE nuclotron, JINR, Dubna, Russia.

A 16

THE USE OF ALANINE / EPR DOSIMETRY IN MEDICAL APPLICATIONS: THE LOW RADIATION DOSE APPROACH

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In the last years, a greater discussion about the use of alanine / EPR dosimetry technique in low dose radiation mapping (diffused radiation) has been focused. This technique is very easy, but has low accuracy for doses lower than 0.5 Gy. A workaround is developing physical and numerical techniques for the EPR signal treatment in order to improve the precision. In this work, alanine/EPR based dosimetry has been used to perform a radiation mapping in different clinical contexts. Four different radiological hospital rooms' environments have been used for test (X-ray diagnostics, Angiography, Digestive Radiology and TAC). A total of 40 dosimeters have been used in fixed points for four months, exposed to the normal room utilization. A calibration curve was obtained over a wide range of radiation doses (from near 0.02 to 1 Gy). A discrete map of diffuse radiation from imagiology/radiology shows the presence of slightly different amount of radiation doses through out the room and in some cases can be correlated with the equipment disposition. Different approach methods for signal fitting and validation have been probed. A complete set of experimental test parameters have been used with a standard dosimeter and the dose reconstruction from numerical simulation can now be used to better adjust the error in calibration curve. The comparison with pure experimental data was made. It is found that the general accuracy limit is less than 50 mGy. With these results, the potential application of alanine in clinical environments is discussed.

A 17

ESTIMATION OF AN RBE VALUE FOR AUGER ELECTRONS EMITTED BY ^{99M}TC

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Decaying 99mTc, frequently used in diagnostic nuclear medicine, does not only emit a gamma ray (140.5 keV), but also Auger and conversion electrons. Determining a radiation weighting factor, these low-energy electrons need a particular consideration because of their extreme short ranges in tissue. For comparison, ultra soft X rays are used here, which deposit their energy in tissue mainly via photoeffect initiating thereby also low-energy photoelectrons and, depending on the kinetic energy, additional Auger electrons. Insofar, the initial physical situation with ultra soft X rays is similar to the case of uniformly distributed Auger emitters.

Monte Carlo computer codes have provided electron emission spectra of 99mTc and, subsequently, track structure calculations were used to simulate the induction of DNA damage of different complexity. For the modelling of ultra soft X rays photon energies of 0.27 (C-K) and 1.5 keV (Al-K) were selected, for which experimental results are available from the literature.

On average, four electrons have been found emitted per 99mTc decay with kinetic energies partly in the same range as those of secondary electrons released by ultra soft X rays. Within a typical mammalian cell volume (sphere diameter of 10 ?m) about 2.5 keV electron energy will be deposited per decay. Relating to the same number of decays or photoeffects, respectively, 99mTc causes a nearly identical spectrum of primary DNA strand breaks as C-K radiation. On this basis, a total radiation weighting factor of 1.2 has been evaluated here for 99mTc.

A 18

FORMATION OF ION CLUSTERS BY LOW-ENERGY ELECTRONS IN NANOMETRIC TARGETS: EXPERIMENT AND MONTE CARLO SIMULATION

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Short segments of the DNA are the main targets for the initiation of radio-biological effects. Because of the nanometric target size, the initiation of radiation damage is caused to the greater part by single particle interactions. For a detailed understanding of radiation-induced effects, therefore, the overlay of the track structure of an ionizing particle and of target volumes of nanometre size has to be taken into account. Since delta electrons contribute to the initiation of radiation damage for all kinds of ionizing radiation, the interaction pattern of electrons at energies up to few keV is of particular importance, including their ability of forming ionization clusters. In view of this fact, it is the aim of the present paper (i) to describe the first experimental data on the distribution of ionisation cluster size produced by low energy electrons in a target cylinder of nitrogen, 3.5 nm in diameter at unit density, which is equivalent to about 2 nm in liquid water, and (ii) to present cluster-size distributions calculated by Monte Carlo simulation. In the experiment, nanometric targets were simulated in the so-called Jet-Counter. It consists of a pulse-operated valve which injects an expanding jet of nitrogen into an interaction chamber where a cylindrical sensitive volume is created. This sensitive volume was irradiated by electrons at 200 eV, 300 eV, 500 eV and 1 keV emitted by an electron gun. The distribution of ionization cluster size was measured using the single-ion-counting method and compared with the results of the Monte Carlo simulation.

A 19

ANALYSIS OF THE SPECIFIC ENERGY DISTRIBUTION AROUND THE TRACKS OF HZE PARTICLES

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Estimation of biological effects due to exposure of HZE particles is one of the key issues in the planning of long-term space missions and heavy ion cancer therapies. Detailed information on the specific energy distributions around their tracks is indispensable in the issue, since the radiation qualities of HZE particles cannot be uniquely determined from their LET because of their large production cross sections of high-energy delta-rays. We therefore calculated the specific energy distributions in liquid water around the tracks of protons and several kinds of heavy ions with energies from 1 MeV/n to 100 GeV/n. The calculations were performed by a Monte Carlo electron track structure simulation code coupled with the Katz's delta-ray production model. In the simulation, the targets were assumed to be spherical sites with diameters from 1 nm to 1 m. An analytical function to reproduce the simulation results has been developed in order to predict the distribution for all kinds of heavy ions with wide energy ranges. By incorporated into the Particle and Heavy Ion Transport code System PHITS, the function enables us to calculate the specific energy distribution in macroscopic matters such as specified organs of astronauts or tumor of patients within a short computational time.

A 20

RADIAL SECONDARY DOSE PROFILES FROM LIGHT ION BEAMS IN WATER CALCULATED WITH A SEMI-ANALYTICAL PENCIL BEAM METHOD

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A semi-analytical pencil-beam method (PB) for fast calculations of lateral dose distributions due to secondary electrons from light ions in water has been developed. A pure Monte Carlo (MC) calculation of the radial dose has also been performed for comparison. A numerical comparison of the radial dose profile between 0.5 MeV p+ and 2 MeV He+ and between 1 MeV p+ and 4 MeV He+ are performed for both methods. The double differential cross sections for secondary electron production were calculated with the continuous distorted waves-eikonal initial state (CDW-EIS) method (kindly provided by G H Olivera).
No attenuation of the point mono-directional mono-energetic ion beam in the interval of calculation is assumed. The dose distribution from the generated electrons is in the semi-analytical case calculated with the Gaussian pencil beam method and simulated with the MC code PENELOPE in the other case. Comparing the results with the general assumed 1/r2 law and other semi-analytical and MC calculations the present PB and MC calculations agrees approximately at intermediate radii, but at small and large radii a shallower and steeper slope is clearly seen for both MC and PB. As expected, the total dose profiles of 0.5 MeV p+ and 2 MeV He+ is very similar up to a radius of 10-8 m, but deviates when the radius increases. A similar behavior is observed for 1 MeV p+ and 4 MeV He+. The primary and secondary electron energy deposit shows the same behavior as the total energy deposit.

A 21

YIELDS OF SOFT X-RAY INDUCED STRAND BREAKS AND BASE LESIONS IN PLASMID DNA

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We have studied yields of DNA damages induced by soft X-rays obtained from a conventional soft X-ray machine in a LET region between -rays and ultrasoft X-rays. Generally, 2-5 MeV -rays are known as typical low-LET photon sources. Ultrasoft X-rays below 10 keV have been considered as relatively higher LET photons such as characteristic X-rays (ex. aluminum-K, 1.8 keV) or monochromatic synchrotron radiation (ex. oxygen K-edge, 0.5 keV). On the other hand, soft X-rays with a broad energy spectrum emitted from a target of heavy metal, such as tungsten (mean photon energy: ~100 keV), have been widely used not only for radiobiological experiments but also for medical application such as mammography. Radiation weighting factors for these soft X-rays have been assigned to be 1 by ICRP. However, the fraction of a large number of low energy photons in the spectrum (below several tens keV) provided by bremsstrahlung in addition to the characteristic X-rays are expected to be more effective for DNA damage induction than -rays since low energy photo- and Auger electrons predominantly ejected in consequence of a photoelectric effect can produce dense clusters of ionization/excitation on DNA molecules. We have examined the yield of DNA strand breaks induced by white soft X-rays (150 kVp, tungsten target, 0.2mm Al filter). Several DNA solutions with different scavenger capacities and also hydrated DNA samples were irradiated to compare the data with the previous ones for -rays and ultrasoft X-rays. Yields of base lesions revealed by base excision repair enzymes will be also presented.

A 22

ELECTRON BEAM TRANSPORT IN HETEROGENEOUS SLAB MEDIA FROM MEV DOWN TO EV

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An optimized Monte Carlo method based on the null collision technique is used for the simulation of the electron transport in multilayer configurations from high energies (MeV or several hundred of keV) down to low cutoff energies (between 1 to 10 eV). The individual treatment of every interaction allows us to correctly consider the boundary interface layer without any mean free path truncation and with a rigorous treatment of the backscattered electrons from a layer to another one. Two layer matters are considered (carbon at 1.7 g/cm3 and polystyrene at 1.07 g/cm3) under two slab or three slab configurations as i.e. a thin layer of carbon sandwiched between two polystyrene layers.
First of all, a careful validation of the used electron-matter cross sections (electron-carbon and electron-polystyrene) is performed in the case of homogeneous media (carbon and polystyrene) for several initial electron beam energies. Then, the perturbation of the energy deposition near the interface media is analyzed. Finally, the large effect of the choice of a low energy cutoff is clearly shown in the heterogeneous slab media more particularly on the electron energy distribution, the secondary electron emission and the inelastic collision number.

A 23

EFFECT OF IONIZATION DISTRIBUTION ON THE OPTICALLY STIMULATED LUMINESCENCE OF AL2O3:C

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The all-optical nature and precision achieved with the Optically Stimulated Luminescence (OSL) technique and the high-sensitivity carbon doped aluminum oxide (Al2O3:C) are finding applications beyond the area of personal dosimetry, in which it is now widely used. The technique has been proposed for space dosimetry and radiotherapy with excellent results, reproducibility better than 1%, and accuracy within 1-2% for radiotherapy applications. This paper presents the effect of ionization distribution caused by different types of particles and energies on the OSL signal of Al2O3:C, in particular the dependence on the ionization density of the efficiency to heavy charged particles relative to 60Co gamma radiation, emission spectrum, and shape of the OSL decay curves. These observations are part of a study of the dosimeter properties after irradiation with heavy charged particles from proton to iron, with energies of a few hundred MeV/u, carried out at the Heavy Ion Medical Accelerator in Chiba from the National Institute of Radiological Sciences (Japan). The usefulness and limitations of these ionization-density-dependent effects for discrimination between the energy deposited in high and low ionization density regions in complex radiation fields are discussed.

A 24

DOSE AS A KEY PARAMETER AND THE LNT HYPOTHESIS IN THE FIELD OF IONIZING RADIATION

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A basic question of current radiation biology, radiation protection and cancer research is the shape of the dose - biological effect curve at low doses. In the literature, significant efforts have been made to answer this question. The reply of the international radiation protection organizations is that the linear-nonthreshold (LNT) relationship should be applied as long as there is not enough information for the exact form of the dose - effect curve. Based on the NCRP 139 Report ("Evaluation of the Linear No Threshold Hypothesis in Radiation Protection") there is not enough arguments and proofs to deviate from the LNT approximation. There are some new arguments that under a given radiation exposure one should neglect the health effects of radiation. The present lecture points to the multi-parameter nature of the analyzed relationships and demonstrates that in general a unified dose - effect curve cannot exist. The reason why the measured parameters show high uncertainty at low doses may originate from this multidimensional feature. At low doses, not the dose but other parameters may have higher role than the dose in the biological responses. Under a particular dose, it is not the dose but other physical, chemical and biological parameters, which basically determine the health effects. Even, this dose limit may depend on the other parameters. The search for these dose limits is an important task. The difficulties in dose - effect relationships at low doses primarily originate from the improper expectations associated with the LNT hypothesis.

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B 1

CALCULATION OF DNA SINGLE STRAND BREAKS BY NEUTRALIZATION EFFECT IN DNA-INCORPORATED 125I DECAYS

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The decay of the radioisotope 125I into 125Te is typically followed by the emission of two groups of approximately 10 electrons each via Auger processes. In deoxyribonucleic acid (DNA) with 125I incorporated, these electrons produce various types of damage to DNA, e.g. single strand breaks (SSBs) and double strand breaks (DSBs) through direct actions of physical tracks, or indirect actions of radicals produced in water. Among the direct actions one should consider not only the excitation and ionization of DNA by Auger electrons but also the neutralization of highly charged 125mTe ions with electrons from neighbouring molecules. Comparison between experiment and simulation done recently revealed that without including neutralization effect the simulated yield of SSBs were 50% less than the measured values. The present work begins with a calculation of neutralization process in a 41-mer synthetic oligodeoxynucleotide (oligoDNA) model. The neutralization contribution obtained by the charge transfer theory based on the new transfer rates using the newly evaluated electronic coupling showed that hole transfer rates are of the order of magnitudes of several 10^{13} s-1, implying that a charge higher than 10 units will not build on a 125mTe atom. The potential energy deposited on the decay base is transferred to bases along the DNA chain nearby and destroys those bases and ionizes the sugar-phosphate group, leading a DNA SSBs with a probability of 0.2% per eV.

B 2

LINEAR PLASMID DNA HAS GREATER SUSCEPTIBILITY THAN SUPERCOILED PLASMID DNA TO DOUBLE-STRAND BREAKS INDUCED BY AUGER ELECTRONS.

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We have investigated the role of DNA compaction and conformation in double-strand-break (DSB) production using pUC19 linear (L) and supercoiled (SC) DNA exposed to 125I-labeled Hoechst 33342 (125IH). Tritium-labeled supercoiled pUC19 was digested with E. coRI and the linearized DNA was purified. The tritiated L and SC DNA were incubated with 125IH (± 0.2 M DMSO) at 4ºC. At various time periods, aliquots were analyzed on agarose gels, and the DSB yields quantified.

The results indicate that the decay of 125I in close proximity to L DNA leads to very different fragmentation patterns in the presence and absence of the ·OH scavenger DMSO. In the former case, distinct bands are seen, whereas in the latter situation, continuous smears are obtained. After incubation with 125IH, the DSB yield for L DNA (DSBL) in the absence of DMSO is 1.60±0.11 per decaying 125I atom; this is approximately 3-fold higher than the DSB yield observed for SC DNA (0.55±0.01) under the same conditions. Furthermore, DMSO leads to a significant reduction in DSBL yield to 0.59±0.07 per 125I decay, indicating that about ~65% of the DSB are caused by indirect effects mediated by hydroxyl radicals. Finally, the yield of DSBL (+DMSO) is about the same as that observed following 125IH decay in SC DNA which originates solely from direct effects.

These data lead us to conclude that 125IH-induced DSB arising from direct ionization of DNA do not depend on DNA compaction (i.e. supercoiling) and conformation (e.g. underwound configuration of SC DNA). Furthermore, it seems that when an ?OH produced by a decaying 125I atom nicks a SC DNA molecule, the release of torsional energy by the latter displaces the nicked region away from the decay site so that either the damaged area becomes totally inaccessible to another ·OH attack or additional SSB formed are too distant from the original SSB to generate a DSB.

C 1

ROLE OF DNA/CHROMATIN ORGANISATION AND SCAVENGING CAPACITY IN USX- AND PROTON- INDUCED DNA DAMAGE

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DNA higher-order structures and (non-histonic) OH radical scavengers have well known protective effects in the induction of single- and double-strand breaks by ionising radiation. In a previous work, such protective roles have been quantified for gamma radiation (Valota et al., Int. J. Radiat. Biol. 79, 2003). As a starting base for the simulations, we used the PARTRAC Monte Carlo code, developed within a collaboration involving the GSF Institute of Radiation Protection and the Nuclear and Theoretical Physics Department of the University of Pavia. The code calculates the track structures of photons, electrons, protons and heavier ions in liquid water, and it describes the DNA content of a human cell at different organisation levels, based on an atom-by-atom approach.

In this work we extended the calculations to Ultra-Soft X rays (USX) and protons, separately analysing the effects of different radiation types on various DNA structures (i.e. naked DNA, SV40 "minichromosomes" and compact chromatin) as a function of the "OH scavenging capacity (SC). Both for USX and for protons, the calculated damage yields decreased by increasing the SC for the three considered target types. Such decrease can be ascribed to the competition between the reactions OH-DNA and OH-scavenger, which becomes more and more likely by increasing the SC. Furthermore, naked DNA was found to be more radiosensitive than SV40 minichromosomes, which in turn were more radiosensitive than compact chromatin, which is protected by histones. Comparisons with experimental data by Fulford et al. (Int. J. Radiat. Biol. 77, 2001) relative to USX irradiation showed very good agreement. The dependence of the modulating role played by DNA organisation and scavenging capacity on radiation quality will be presented and discussed.

C 2

DNA-REPAIR PROTEIN DISTRIBUTION ALONG THE TRACKS OF ENERGETIC IONS

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The irradiation of nuclei in living cells with energetic ions allows to generate DNA double strand breaks in a definable manner. Subsequent DNA repair processes in the cell accomplished by dedicated proteins can be studied using immunofluorescence techniques. To investigate the damage structure along the ion track it is advantageous to perform microscopical examination perpendicularly to the track direction in order to obtain high optical resolution. Therefore the Munich ion microprobe setup SNAKE (superconducting nanoprobe for applied nuclear (Kern-) physics experiments) was used to irradiate HeLa cells under an angle of 10° between beam direction and cell substrate. The irradiation was done with 29 MeV 7Li ions (LET in H2O: 86 keV/µm) resp. 24 MeV 12C ions (LET in H2O: 525 keV/µm). Software deconvolution of fluorescence microscope image stacks delivered three dimensional data of 53BP1 protein distribution which then was visualized using rendering software. The number of fluorescent foci per unit path length for the two ion beams was compared to a elementary model of chromatin distribution in the cell nucleus.

C 3

TRACK STRUCTURE MODELLING OF THE HEAVY ION RESPONSE OF THERMO-LUMINESCENT DETECTORS

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We use Katz's track structure model and a 2-hit and/or 1-hit TL trap decomposition of the Co-60 dose responses (measured up to signal saturation) of MTS-7, MCP-7 and MTT-7 thermoluminescent (TL) detectors, to calculate the effectiveness, relative to Co-60 gamma-rays, of these detectors exposed to low fluences of He, C, Ne, Fe, Si, Ar and Kr ions of energy between 100 MeV/amu and 500 MeV/amu from the HIMAC accelerator, within the ICCHIBAN series of experiments. Following some much earlier work, we relate the enhanced relative effectiveness of MTS-7 and MTT-7 to the presence of supralinearity, as represented by the 2-hit trap contributions in their gamma-ray response. We expect our model calculations to be applicable to the interpretation of the results of a long-term open space exposure of these detectors inside a humanoid phantom, within the MATROSHKA experiment.
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C 4

CLUSTER SIZE DISTRIBUTIONS FOR ALPHA PARTICLE IN WATER: EXPERIMENT AND MODELLING

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We present data on clustered damage formation by charged particles in biological medium using experimental, theoretical and simulation methods. Theoretical and simulation data, generated in water as a surrogate for biological tissue, were compared with the experimental results. The theoretically derived cluster size distributions for alphas-particles were obtained using the K-means algorithm. The experiments were carried out with a beam of 4.6 MeV alpha-particles performed in a setup called the JET Counter. The simulations were done by Monte Carlo track structure calculations. The first moment of cluster size distributions for water, derived from K-means algorithm as a function of diameter of cluster centroid, were compared with the corresponding moments derived from the experiments for nitrogen and propane targets. The slope of the first moment of the distribution as a function of target diameter was obtained. It was found that the ratio of first moments for water to gas targets correlates well with the corresponding ratio of mean free paths for primary ionisation of alpha-particles in the two media. It is shown that the cluster size distributions for alpha-particles in water, obtained from K-means algorithm, are in agreement with the corresponding distributions measured experimentally in nitrogen or propane gas targets of nanometer sizes.

C 5

MONTE CARLO SIMULATIONS OF DNA STRAND BREAKS BY LOW ENERGY ELECTRONS

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Monte Carlo (MC) simulations of the DNA strand breaks induced by low energy electrons were performed. An event-by-event MC code was developed for the simulation of electron tracks and energy depositions in liquid water. The code followed the history of primary and secondary electrons, interaction by interaction, until all electrons were thermalized. The differential inverse mean free paths for inelastic interactions were calculated using the dielectric response theory. The differential cross sections for elastic interactions were computed using the quantum mechanical phase shift analyses. The DNA duplex was modeled by a representation of the sugar-phosphates with two parallel cylinders to evaluate direct and indirect actions. Any energy deposition greater than 17.6 eV in the cylinder was assumed to generate a single strand break (ssb) by the direct action. For the indirect action, a threshold energy deposition of 12.6 eV in the cylindrical shell 0.5 nm around the cylinder was required for the induction of OH radical. The probability of this radical causing a strand break was set to 0.13. When two ssb occurred on opposite strands separated by 10 or fewer base pairs, a double strand break (dsb) was produced. Assuming DNA cylinders of diameter 0.5 nm and separation 1 nm, the probability of dsb was around 0.14 per electron (250 eV) emission from the center of the DNA structure. This probability decreased to about 0.06 per electron (550 eV) emission from the same position. For electron emission from the outer surface of the DNA cylinder, the probability decreased to 0.01 and 0.03 for 250 and 550 eV electron emissions.

D 1

A COMPARISON OF CELLULAR IRRADIATION TECHNIQUES WITH ALPHA PARTICLES USING THE GEANT4 MONTE CARLO SIMULATION TOOLKIT

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In vitro cellular irradiation techniques provide a unique opportunity to investigate at the cellular scale the biological effects of low dose irradiation by ionising particles and could contribute to a better understanding of the low dose risk to human health. For this purpose, several experimental techniques have been developed worldwide. A comparison of three in vitro cellular irradiation techniques using the Geant4 Monte Carlo simulation toolkit is presented. The experimental techniques described involve electrodeposited sources of alpha particle-emitting radionuclides (238 Pu - 239 Pu), random classical beam irradiation using an alpha particle broad beam delivered by a 7 MV Tandem accelerator - both developed in Bruyères-le-Châtel, France (CEA/DIF/DPTA/SP2A) - and single cell targeted irradiation using a focused alpha microbeam line installed on a 3.5 MeV Van de Graaff accelerator and developed at the Centre d'Etudes Nucléaires de Bordeaux-Gradignan, France (CNRS/IN2P3, Université Bordeaux 1). The simulation allows the calculation of hit distributions among the cellular population as well as the absorbed dose for reasonable cellular geometries. It offers a refined alternative to analytic models.

D 2

CELLULAR S-VALUES AND LINEAL ENERGIES FOR ELECTRONS

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Calculations of the cellular microdosimetry parameters, including the cellular S-value and the lineal energy, for electrons were performed for various combinations of source and target regions, i.e. cell surface (CS), cytoplasm (Cy), cell nucleus (N) and cell (C). The S-value and the lineal energy represent, respectively, radiation quantity and quality in cellular microdosimetry. Both analytical and Monte Carlo (MC) approaches were established for these calculations. In the analytical approach, partial delta-ray equilibrium, CSDA range-energy relation, Landau energy loss straggling, and bremsstrahlung were adopted or considered for transport electrons in liquid water. For the MC approach, the mixed algorithm (event-by event simulation of hard collisions; multiple scattering approximation of soft collisions) Penelope code was used. Calculated cellular S-values were compared with each other and to published MIRD data. Analyses were made with respect to electron energy, source-target geometry and size, and contributions from elastic collisions, inelastic collisions and bremsstrahlungs. In the case of source-target combination N<-Cy and N<-CS, for instance, the cellular S-value was mainly contributed from stoppers and crossers for, respectively, low and high energy electrons. For source-target combination N<-N and C<-C, the cellular S-value was mainly contributed from insiders and starters for, respectively, low and high energy electrons. The frequency mean lineal energy depended on electron energy, source-target geometry, and target size. For source-target combination N<-N, for instance, the maximum frequency mean lineal energy occurred at electron energy ~ 10 keV where the CSDA range was close to the target size.

D 3

RADIOBIOLOGICAL MODELS IMPLEMENTATION IN GEANT4 TOOLKIT

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A project is in progress to extend the Geant4 simulation toolkit to model the effects of radiation with biological systems, both at cellular and DNA level. For the first time a general-purpose Monte Carlo system is equipped with functionality specific to radiobiological simulations.
The object oriented technology adopted by Geant4 allows providing an ample set of models to simulate the response of a cell line to irradiation, leaving the option to users to choose among them the most appropriate ones for their simulation study. The project follows an iterative and incremental software process; the first component implemented describes a primary biological endpoint: the fractional survival of a population of cells irradiated with photons or charged particles. It provides the user the option to choose among a wide set of cell survival models, such as models based on the target theory of cell killing, the repair-misrepair model, the lethal-potentially lethal model, and the Scholz and Kraft model. The flexible design adopted makes it open to further extension to implement other cell survival models.
We present the architecture of the new Geant4 component for radiobiological modeling, the detailed design of the cell survival models implemented and preliminary results of application in some specific cell lines. The simulation tool developed for the study of radiation interaction with biological matter would have a wide domain of application in several fields: from oncological radiotherapy to the radiation protection of astronauts.

F 1

PERMANENCE OF HISTONE H2AX PHOSPHORYLATION IN HUMAN FIBROBLASTS EXPOSED TO VARIOUS RADIATION QUALITIES

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One of the more interesting chromatin modification events which occur after a DNA double strand breaks (DSB) induction in higher eukaryotes, is the phosphorylation of the SQ motif found in histone H2AX variant. Phosphorylated H2AX histone (H2AX) clusters can be visualized as foci by immunofluorescence using phospho-specific antibodies. This technique allows us to detect even a single DSB in the DNA, proving to be a useful tool to study DNA DSB induction and repair at low doses. In the present work we report on the H2AX phosphorylation-dephosphorylation kinetics after irradiation of human fibroblasts with g-rays, carbon ions and alpha particles, in order to analyze the DSB induction and repair as a function of radiation quality.
Different phosphorylation-dephosphorylation kinetics were observed after irradiation with the radiations considered in this study; in particular, for repair times longer that 2 h, more foci remained in cells irradiated with carbon ions than in those irradiated with the same dose of g-rays, and even more in those irradiated with alpha particles. This findings indicate that foci persistence is dependent on radiation quality. Besides, the maximum number of foci, which was comparable to the calculated number of particle traversals giving at least 1 DSB, is reached later after irradiation with carbon ions and alpha particles.
Taken together our findings are consistent with the presence of a more complex and clustered damage induced by charged particles that is more severe and difficult to repair with respect to that induced by g-rays.

F 2

PROFILE OF RADIATION SENSITIVITY IN DIFFERENT HUMAN CELL TYPES

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In this study we aim to profile the transcriptional alterations induced by radiation in human transformed and non-transformed cells. In order to characterize the general response to ionizing radiation to be able to discriminate between the response of normal and malignant cells. In summary the transcriptional responses to ionizing radiation are to a large extent cell-type specific. A predominant role of the tumor suppressor protein p53 in signaling the radiation damage in normal cells has been confirmed. Although alternative pathways have been identified in malignant cells or p53 mutated. The ultimate goal of this work is to maximize the effect of radiation therapy on malignant cells with the best possible protection of normal cells. Modulation of specific pathways with appropriate cytokines and growth factors might help to encounter the undesired negative effect of ionizing radiation on normal cells, while enhancing the damage in malignant cells.

F 3

DNA DAMAGE AND REPAIR FOLLOWING NITROGEN ION IRRADIATION AS A FUNCTION OF CELLULAR DIFFERENTIATION IN K562 CELLS.

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To investigate whether the response to radiation damage is dependent on cellular differentiation, we have studied the induction and rejoining of the DNA DSB in proerythroblastoid cell line K562 before and after differentiation. The cells were irradiated with 125 keV/ um N ions at Gustaf Werner synchrocyclotron of Bio-Medical Unit at the Svedberg Laboratory, Uppsala. 60Co g-rays were used as reference radiation. Calibrated Pulsed Field Gel Electrophoresis (PFGE) was used to analyze DNA fragments in the size range 5.7 - 0.023 Mbp, using two different conditions able to separate fragments in the size range 5.7 - 1.0 Mbp and 1.0 - 0.145 Mbp. This technique allows determination of the fragment size distribution as well as of the number of DNA DSB.
Here we report on the results obtained during several years on K562 cells. They show that chromatin structure can affect the DNA damage induction and repair after exposure to ionizing radiation. Also, radiation quality was shown to be important, suggesting a complex interaction between track structure and chromatin organization.

F 4

THE SENSITIVITY OF THE ALKALINE COMET ASSAY IN DETECTING DNA LESIONS INDUCED BY X RAYS, GAMMA RAYS AND ALPHA PARTICLES

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Single cell gel electrophoresis, also known as comet assay, has been shown to be a sensitive method for the analysis of induction and repair of DNA strand breaks and oxidative DNA lesions. The alkaline comet assay was applied here to detect DNA breaks induced by different types of radiation. The goal was to demonstrate if different energy deposition patterns of photon radiation with varying energies (29 kV, 220 kV X rays; Co-60 -, Cs-137- g-rays) and alpha-radiation from an Am-241 source and from Bi-213 bound to antibodies against the cellular adhesion molecule E-cadherin result in DNA lesions, which can be quantified by the comet assay either by the radiation specific dose effect relationship or their repair kinetics. Radiation experiments were performed with human lymphocytes exposed to X and gamma rays (0.5 Gy - 3.0 Gy) and with a human gastric cancer cell line (HSC45-M2) exposed to alpha particles (Am-241: 0.5 - 3.0 Gy; Bi-213: activities from 1.6 MBq - 9.9 MBq). Cs-137- g-rays were used as a reference radiation. DNA damage was quantified by three parameters: %DNA in the tail, tail length and tail moment according to Olive. Data were fitted and compared using a multiple linear regression model. The comet assay data for %DNA in the tail and tail moment did not indicate any difference in the initial radiation damage produced by 29 kV X rays relative to the reference radiation types, 220 kV X rays and the gamma rays, either for the total dose range or in the low-dose range. In contrast, when fits of tail length data were performed, saturation appears for X rays but not for gammas. The exponential term, which models the bending over the dose response in the fit, is significantly different from zero for the X rays but not for the gamma rays. This result may be interpreted to indicate that X rays induce smaller DNA fragments or more strand breaks at low doses. Best-fit calculations for the repair kinetics do show a tendency that for irradiation with 29 kV X rays, repair of damaged DNA proceeded slightly more slowly in the first 10 to 20 minutes but this result was not statistically significant. Data for both alpha exposures showed a significant increase in DNA damage only at high doses (>2 Gy Am-241; >1.6 MBq Bi-213), but the damage at 2 Gy exceeded the damage induced at 2 Gy by Cs-137- g-rays by a factor of 2.5. Experiments involving other DNA damage indicators such as chromosomal aberrations detect a significant increase in DNA damage at much lower doses, i.e. at 0.02 Gy Am-241 or 18.5 kBq of Bi-213. These results indicate that differences in biological effects must arise through downstream processing of complex DNA damage, which is not detected by the alkaline comet assay.

F 5

CO-LOCALISATION OF -H2AX AND 53BP1 TO SITES OF DNA DOUBLE STRAND BREAKS FOLLOWING HIGH LET IRRADIATION OF MAMMALIAN CELLS.

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When cells are exposed to ionising radiation lesions are introduced into the DNA including single strand breaks (SSBs), double strand breaks (DSBs) and base damage together with clustered DNA damage sites, a specific feature of radiation induced DNA damage. An early step in the response of mammalian cells to radiation induced DSBs is the substantial phosphorylation of the histone H2AX at sites of DNA DSBs. p53 Binding Protein 1 (53BP1) has also been shown to localise to sites of radiation induced DNA DSBs and it appears that H2AX phosphorylation (g-H2AX) is required for the formation of 53BP1 foci at sites of DSB. The activation and foci formation of these proteins can be utilised to visualise radiation induced DNA DSBs at low doses by using immunofluorescence. We have investigated the induction and repair of DNA DSBs in exponentially growing hamster cells (V79-4) by radiation of different quality (low LET g-rays and high LET a-particles). A linear induction of g-H2AX foci was observed with dose (20-2000mGy) following either g- or a-irradiation. The loss of g-H2AX foci for a-irradiation follows the rejoining of DSBs as demonstrated by PFGE. Co-localisation studies following a-radiation demonstrate that the majority of 53BP1 foci (80-90%) co-localise with g-H2AX even at early times; however, a large proportion of g-H2AX foci are not co-localised with 53BP1. These results suggest that not all sites of DNA DSBs (as determined by g-H2AX foci formation) lead to the recruitment of 53BP1 following high LET irradiation.

F 6

ANALYSIS OF DAMAGE INDUCTION AND REPAIR PROCESSES AFTER CARBON IRRADIATION IN DIFFERENT CELL LINES

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Detailed characteristics of damage induction and repair processes can be derived by analyzing survival data using the probabilistic two-stage model (Kundrát et al, Phys. Med. Biol. 50, 1433-1447, 2005). We will present the results of the analysis of cell survival data for three Chinese hamster cell lines, wild-type V79 and CHO-K1 cells and repair-deficient CHO mutant xrs5, irradiated by carbon ions (Weyrather et al, Int. J. Radiat. Biol. 75, 1357-1364, 1999).
The differences in radiation response between xrs5 and CHO-K1 cells have been attributed to their different repair capacities, the damage formation characteristics being the same. For the sake of simplicity, only damages unrepairable by the xrs5 cell line have been considered, i.e. the repair has been neglected completely in xrs5 cells, while it plays an important role for CHO-K1 cells. The results reflect the fact that the xrs5 cell line differs from CHO-K1 cells in lacking Ku80 component of the active DNA-PK complex, which leads to its deficiency in DSB repair.
Results of similar analyses performed for other experimental data sets will be presented, too.

F 7

HEAT SHOCK TRANSCRIPTIONAL FACTOR 1 (HSF1) CONTRIBUTES TO RADIOADAPTIVE RESPONSE INDUCED BY LOW DOSES OF GAMMA-IRRADIATION

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The radioadaptive response in cells following low-dose-radiation exposure is a well known phenomenon whose molecular mechanism is, however, not quite clear. As the heat shock transcriptional factor 1 (HSF1) plays a prominent role in stress-responsive and cytoprotective mechanisms, the aim of this study was to examine whether HSF1 contributes to the low-dose-radiation-induced radioadaptive response. For this purpose, mouse embryo fibroblasts with HSF1-gene knockout (HSF1 -/- cells) or, otherwise, with normal wild-type HSF1 expression (HSF1 wt cells) were exposed to gamma-irradiation, first, at a priming low dose (1 cGy) and then, after 6-8 hours, at a challenging high dose (5 Gy). Some cell samples were infected with special virus-based vectors to overexpress the constitutively active (mutant) form of HSF1 or individual heat shock proteins (Hsps). Under entirely equal conditions, the radioadaptive response (i.e. low-dose-radiation-induced resistance to high doses of irradiation) was much better manifested in the HSF1 wt cells which, being pre-irradiated at the low dose, expressed Hsp70 and Hsp27 following the high-dose irradiation. However, when the constitutively active HSF1 was overexpressed in HSF1 -/- cells, the latter also expressed the inducible Hsps and became more radioresistant like pre-irradiated HSF1 wt cells. Similarly, the overexpression of Hsp70 or/and Hsp27 significantly enhanced radioresistance of either cell culture. Taken together, these data demonstrate that the HSF1-mediated Hsp induction can contribute to development of the radioadaptive response resulting from pre-irradiation with low doses. On the other hand, HSF1 may contribute to maintaining of the genome instability by promoting survival and propagation of radiation-affected cells.

F 8

MUTATION INDUCTION IN HUMAN CELLS BY 60CO GAMMA RAYS AND 30 KV X-RAYS

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Mutations were studied at the HPRT-locus in MGHU-1 (human male bladder carcinoma) cells after exposure to filtered 30 kV X-rays and 60Co gamma rays. Mutant frequencies were found to increase in a linear-quadratic fashion with dose in both cases. If only the low dose part is analysed: a RBE of 2.05+0.46 is obtained. PCR analysis was also here performed. There is a clear tendency that the fraction of deletions is increased with lower photon energies but the effect is not significant. Translocations of the q-arm of the X-chromosome where the HPRT-gene is located were also determined. With 30 kV X-rays 17% out of 53 analysed mutant clones showed translocations (95% confidence interval: 9..30). The respective numbers for gamma-induced mutants (25 clones) are 12 (confidence interval: 4.6..31). Although the lower photon energy induces more translocations the difference is again not significant. The low fraction with translocations leads to the conclusion that only a minor part of mutants with no detectable deletions can be attributed to translocations.

F 9

DETAILED ANALYSIS OF CELL INACTIVATION MECHANISM BY DIFFERENT IONS

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Biological effects of protons and light ions have been studied in detail by analyzing published cell-survival data with the help of the probabilistic two-stage radiobiological model. Probabilities of single ions to induce damages of different severity have been assessed in dependence on their linear energy transfer. The results will be presented and their interpretation in terms of Zeff2/b2 (the effective charge over velocity squared) and other track-structure characteristics will be discussed. Applications in hadrontherapy will be outlined.

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F 10

INVESTIGATION OF THE EFFECT OF BASE LESIONS ON THE REJOINING OF DOUBLE STRAND BREAKS (DSBS) WHEN IN CLOSE PROXIMITY TO THE DSB

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DSBs are amongst the lesions induced by ionising radiation and are often associated with one or more base lesions (complex DSB), with their complexity increasing with ionisation density. DSB, simple or complex, can lead to loss or alteration of genomic information with possible deleterious effects for the organism. In mammalian cells the Non-Homologous End Joining pathway (NHEJ) is the major pathway used to repair DSBs, however, evidence supports a reduced repairability of complex DSB in cells. In addition, previous studies suggested that the presence of 8-oxoG close to DSB termini of synthetic oligonucleotides inhibits the ligation of the broken ends by T4 ligase.

The aim of this project is to investigate whether DNA lesions close to DSB termini affect their rejoining, by developing a DNA assay to evaluate the processing of complex DNA DSBs. In this assay oligonucleotides with 8-oxoG close to a restriction site were inserted into a plasmid. Following restriction within the oligonucleotide sequence, a DSB is created with 8-oxoG lesions 2, 4, and 6 bases from the DSB termini. The restricted plasmid was then mixed with HeLa whole cell extracts (WCE) to assess the efficiency of the repair machinery. In addition, the accuracy of the DNA repair was also investigated.

The presence of 8-oxoG close to the DSB termini reduces the efficiency of DSB rejoining, however, the position of the lesion does not influence the extent of the reduction in the efficiency of the DSB. It was also found that only about 50% of the DSB were re-joined faithfully.

These results demonstrate the importance of the effect of complex DSB on the efficiency of the NHEJ pathway and give insights into the mechanisms of the biological consequences of DSB induced by ionising radiation.

F 11

MUTAGENIC POTENTIAL OF 8-OXOG WITHIN CLUSTERED DNA DAMAGE SITE IN ESCHERICHIA COLI.

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Clustered DNA damage induced by a single radiation track is a unique feature of ionizing radiation. Recent in vitro studies have shown that the repair of lesions within clusters may be retarded, but less is known about the mutagenic effects of such clustered damage in vivo. We have investigated the mutagenic potential of bistranded clustered damage sites which consist of 8-oxo-7,8-dihydroguanine (8-oxoG) and dihydrothymine (DHT). Using a bacterial plasmid-based assay, we found a significantly higher mutation frequency for the clustered DHT + 8-oxoG lesions than that for a single 8-oxoG in wild-type in glycosylase-deficient strains of E. coli. MutY activity was very important for reducing the formation of mutations especially from clustered damage. These results suggest that Fpg activity is compromised for removal of lesions within clustered damage sites whereas MutY is efficient post-replication when the damaged sites are no longer clustered. The mutation frequency increases as the inter-lesion distance decreases, especially when the lesions are placed 5' to each other, indicating that damage repair is affected by both inter-lesion distance and lesion orientation. The predominant mutation is a G:C?T:A transversion at the position of the 8-oxoG lesion, implying that the excision of lesions is sequential. Interestingly, we found that many of the recovered plasmids from each clone gave rise to both wild-type and mutant progeny in varying proportions. We suggest that, amongst several compounding factors, differential replication of the two DNA strands is in part responsible for the broad range of mutation frequencies observed for these individual clones.

F 12

DNA-TARGETED IONIZING RADIATION RESULTS IN CONSIDERABLY FEWER DIFFERENTIALLY EXPRESSED GENES THAN WHOLE CELL IRRADIATION

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It is generally considered that DNA is the key cellular target of ionizing radiation
(IR) and that DNA damage is the prerequisite for the majority of cellular responses to IR. To test if this is the case for the changes in global gene expression produced by IR we exposed normal human fibroblasts to either gamma-radiation or labeled their DNA with 125I-deoxyuridine (125IUdR), thus, confining radiation damage to the cell nucleus. Gamma-radiation was delivered either at a high-dose rate (HDR, 1 Gy, 1 min) or at a low-dose rate (LDR, 1 Gy, 22 hrs). Differences in the expression of more than 41,000 transcripts were assessed using DNA microarrays. We found that more than 2000 genes were
consistently up- or down-regulated following HDR and LDR gamma radiation. The profiles of differentially expressed genes following HDR and LDR shared about 64 % (up) and 74 % (down) genes in common, with many genes detected as radiation-responsive for the first time. In contrast, only 206 genes in the human genome were differentially expressed in 125IUdR-treated cells. With few exceptions, the expression levels of 125IUdR-responsive genes were also altered following gamma-irradiation. The results suggest that radiation damage of DNA is not a major factor modulating gene expression changes following irradiation, and that factors residing outside the nucleus may play a crucial role in this process.

F 13

ENHANCED CHROMOSOMAL ABERRATIONS IN TUMOR CELLS CAUSED BY CU-K SHELL IONIZATION

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This study aims to investigate the chromosomal aberrations induced by Auger electrons emitted from copper (Cu) atoms in tumor cells. Bone cancer cultured cells, U-2OS, involving non-labeled Cu-pyruvaldehyde-bis(N4-methylsemicarbazone) (Cu-PTSM) was used and the cells were irradiated with monochromatic X rays having energy of Cu-K shell absorption edge arising from synchrotron radiation (PF KEK, Tsukuba). Energies of X rays used for irradiation were 8.944 keV (CuK-L) and 9.034 keV (CuK-H) corresponding to slightly below and slightly above the Cu-K shell absorption edge (8.985 keV), respectively. Chromosomal aberrations, especially isochromatid breaks were evaluated as radiation effect by the method of chemical PCC with calyculin A. The repair kinetics of isochromatid breaks from just after the irradiation until 4 hrs was examined also using the same method. Reference irradiation with conventional 200 kVp X rays was performed to evaluate the effect caused by Cu-K X rays. The enhancements of the yields of isochromatid breaks were observed clearly depending on the Cu-PTSM concentration only when cells were irradiated with Cu-K X rays. At the exposure on the cells after soaking in a medium with 1000 nM Cu-PTSM, the enhancement ratio of the yield of isochromatid breaks caused by the CuK-H X rays irradiation to that by 200 kVp X rays was about 2.8, while, at the exposure to the CuK-L X rays, the enhancement ratio was about 1.9. Thus our data indicate clear enhancements of isochromatid breaks in tumor cells using PET agent of Cu compound and irradiation with Cu-K shell monochromatic X rays, suggesting a possibility of new cancer therapy. This study presents clearly some evidences about the relation between a physical phenomenon such as Cu atom K-shell ionization and a biological phenomenon such as chromosomes damage in cells.

G 1

DIFFERENCE OF DNA DAMAGE INDUCED BY ULTRASOFT X-RAYS AROUND OXYGEN K-EDGE FROM THAT BY CO-60 GAMMA-RAYS

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Short track electrons emitted from DNA constituent atoms after irradiation with ultrasoft X-rays (USX) have been suggested to tend to form severe DNA damage. The aim of this study is to clarify the difference of DNA damage induced by USX from that by Co-60 gamma-rays. In particular, we have recently attended to unaltered base release and strand break pattern, focusing on the effect of oxygen K-electron ionization. HPLC analysis was performed to determine the yield of unaltered bases released. As a result, the yields of them generally increase in the order, gamma-rays < 526 eV (below oxygen K-edge) < 555 eV (above oxygen K-edge) photon. Moreover, to characterize the sites of the strand breaks, the digestion rates of the irradiated DNA pretreated with or without calf intestinal alkaline phosphatase by snake venom phosphodiesterase (SVPD) were measured. This experimental system revealed that the production of the termini, which can be digested by SVPD (SVPD- digestive termini, e.g, with 3' OH) for USX, was clearly predominant in comparison with that of SVPD- resistant ones, e.g., with 3'-phosphate, whereas the ratio of the SVPD- digestive termini to the SVPD- resistant ones, was approximately one for gamma-rays. These results suggest that the differences in the base release yields and the strand break pattern would depend mainly on the secondary electron energy spectrum in the direct radiation effect on DNA.

G 2

DNA FRAGMENTS INDUCTION BY RADIATIONS OF DIFFERENT QUALITIES: EXPERIMENTAL AND THEORETICAL RESULTS.

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The microscopic pattern of energy deposition in matter by charged particles is believed to produce spatially correlated damage in cellular DNA. This kind of damage depends on radiation quality and is very critical for radiobiological effects.
We have studied the DNA Double Strand Breaks (DSB) induction and distribution in human fibroblasts (AG1522) by several doses of gamma-rays, 0.84 MeV protons, 60 MeV/u carbon ions and iron ions of different energies (200 MeV/u, 500 MeV/u, 1 GeV/u and 5 GeV/u). Measure of DNA DSB was performed by Pulsed and Constant Field Gel Electrophoresis (PFGE/CFGE) using different conditions to separate DNA fragments of different size (ranging from 1 to 5700 kbp). DSB yield was evaluated by fragment counting.
In order to perform a quantitative evaluation of the deviation from randomness of the radiation-induced DNA fragmentation an analytical method was implemented.
Our results show that the DSB yield corresponding to the induction of DNA fragments in the range 23-5700 kbp is similar among the different charged particles used and slightly higher than that obtained using gamma-rays. However, calculations showed that the deviation from randomness of DSB induction depends on radiation quality, being higher for the most densely ionizing charged particles and not significant for gamma rays.
When 1-23 kbp fragments were considered, a radiation quality dependent increase in the

G 3

ON THE INTERPRETATION OF THE SINGLE-TRACK LETHAL DAMAGES

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LET-dependent probabilities of single proton tracks to form lethal damages in V79 cells have been derived by analyzing published survival data with the help of the probabilistic two-stage model. The results have been compared to estimated yields of complex DNA double-strand breaks calculated by Monte Carlo models. Good agreement has been found between these two methodologically different approaches, quantifying the correlation between damage complexity and lethality.

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G 4

CLUSTERED DNA DAMAGE INDUCED BY HELIUM IONS OF DIFFERENT LET

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Ionizing radiation causes various types of DNA lesions, such as strand breaks, oxidative base lesions and, in particular, biologically relevant complex damage known as cluster damage sites, which consist of two or more elemental lesions within one or two helical turns of DNA. Clustered DNA damage sites are less readily repaired than are isolated lesions and therefore may induce serious genetic changes in living cells. We present here evidence showing that the yields of DNA lesions and clustered DNA damage induced by He ions strongly depend on their LET. In this study, hydrated plasmid DNA was irradiated at 5.6°C with He2+ ions, which have an initial energy of 50MeV. LET values were changed by inserting Ni-foils to obtain 19, 63 and 95 keV/μm and DNA damages were detected by gel electrophoresis. The yields of prompt single strand-breaks (ssbs) are very similar at the varying LET values, whereas the yield of prompt double-strand breaks (dsbs) increases with increasing LET. These results indicate that closely spaced strand breaks are more readily induced at higher LET. Further, base lesions and clustered damage were revealed as additional strand breaks by post-irradiation treatment of the DNA with endonuclease III (Nth) and formamidopyrimidine-DNA glycosylase (Fpg). The reduction in the yield of these enzymatically-induced ssbs and dsbs becomes significant as the LET increases. These results suggest that the clustering of DNA lesions becomes more probable in regions of high LET.

G 5

SIMULATION OF CLUSTERED DNA DAMAGE INCLUDING BASE DAMAGE USING MONTE CARLO TRACK STRUCTURE METHODS

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Ionizing radiation creates simple and complex patterns of damage within two helical turns of the DNA by a single track. The closely packed patterns consisting two or more damages are called clustered DNA damage. Although DSB has been considered to be the critical damage, recent studies have shown that clustered DNA damage involving base damages may play an important role in biological consequences of radiation damage in the form of mutagenesis and cell killing. The purpose of this study is to estimate the spectrum of initial damage consisting of strand breaks and base damages for ionizing radiations of different linear energy transfer (LET). Induction of strand breaks and base damages were simulated in cell mimetic condition using detailed Monte Carlo track structure methods for atomistic model of DNA. The number and configuration of damages on the DNA segment of a few helical turns of DNA were estimated. The calculations show the contributions to the spectrum of damage involving more than 2 damages to be about 10% for 100 keV electrons and 40% for 1 keV electrons, while it is >60% for 3.2 MeV a-particles. The contributions involving more than 3 damages are 2%, 15% and 45% for 100keV and 1keV electrons and 3.2MeV a-particles, respectively. The detail of the positional distribution of damages which could be related to the inhibition of repair processing will be presented.

H 1

IONIZING RADIATION INDUCES MET TRANSCRIPTION AND INVASIVE GROWTH

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Radiotherapy is one of the major adjuvant treatments for many malignant tumors including breast cancer. The rationale for radiotherapy is based on findings indicating that ionizing radiation (IR) induces apoptotic cell death and inhibits cell proliferation in vitro and tumor growth in vivo. Recently, however, concerns have been raised about the possibility that IR might paradoxically promote cell invasion and metastasis.
A key protein controlling invasive growth is Met, the tyrosine kinase receptor for hepatocyte growth factor (HGF). The Met promoter is inducible by extracellular cues and stress stimuli such as oxygen deprivation. (1)
It has been previously demonstrated that IR may cause Met overexpression and increased motility of pancreatic and neuroblastoma cell lines. We confirmed that IR modulates Met expression in breast cancer cell lines. In cells expressing basal levels of Met, clinical doses of IR (2-10 Gy) induce both Met mRNA and protein in a time-dependent manner, peaking twelve hours after treatment. Interestingly, IR can not induce MET expression in cells negative for MET in basal conditions. Using the isolated promoter in in vitro reporter assays, we show that the mechanism of Met induction involves transcriptional regulation. Consistently, breast cancer cell lines treated with IR display increased cell motility and invasion in vitro. These data provide the first evidence of a direct effect of IR on MET transcriptional control, and suggests a possible mechanism through which IR can increase the risk of metastasis.

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H 2

ARE UN-REJOINED CHROMOSOME BREAKS ALWAYS THE RESULT OF AN IRREPARABLE LESION?

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According to classical cytogenetic theory, a simple chromosome exchange results when two chromosome breaks that are in close proximity with respect to space and time interact by joining broken ends inappropriately, i.e. to wrong partners. On occasion this process is incomplete, leaving what amounts to an "open" chromosome break. We examined the production of complex chromosome exchanges (those formed from three or more breaks) following irradiation of human lymphocytes with either g-rays or HZE particles. We found that breakpoints associated with complex exchanges were 3 to 4.5 times more likely to remain open than breaks forming from simple exchanges. A similar result was observed when plateau-phase fibroblasts were irradiated with g-rays. However, when these cells were irradiated with a-particles, complex exchange breakpoints were nearly as likely to remain open as simple exchange breakpoints. A complex exchange rejoining pathway can be described as cyclical chain of events, with each break involved having a specific spatial relation with the other breaks within the exchange cycle. To explain our results, we propose that while a particular break might be close enough to interact with some members of the rejoining cycle, others may be too distant, rendering the exchange incomplete if nearby partners have already rejoined. Moreover, since the nuclei of plateau-phase fibroblasts are quite thin and flat compared to that of lymphocytes, we imagine that the distance between breaks might lessen the chance of incompleteness for high LET particle traversals. This research was supported by DOE, Grant No. DE-FG03-02ER63442 and NASA/OBPR.

H 3

X-RAY-ASSOCIATED G TO A TRANSITION AT NON-CPG SITE WITHIN C-TERMINAL DOMAIN OF THE HUMAN P53 GENE

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Tumor-specific mutational spectra in the p53 mutation database provide implication for mutagenic events in human carcinogensis. Ionizing radiation (IR) is a mutagenic carcinogen by causing genomic DNA damage, leading to the genomic instability. Among the plethora of genes that are altered in human cancers, the tumor suppressor p53, "guardian of genome", occupies a special place because it is the most frequent target for abnormalities in every type of cancer. To understand the contribution of radiation-associated p53 mutation to cancer development, we investigated the acute and latent mutation spectra of the p53 gene after X-ray exposure in cell lines with different endogenous p53 status. Base-pair transitions are the most observed (60%). Interestingly, 67% of the transitions are G-A transition which localized exclusively at not-CpG sites, but the tetra/penta-purine AAGG/AAGGG sites of the p53 gene coding region. In addition, 60% (9/15) of the detected alterations were scattered within C-terminal domain of p53. Of those, 78% are located within exon 11, suggesting a X-ray-sensitive region of the p53 gene. Interestingly, no mutation could be found 5 days after exposure in cell lines with functional wild-type p53, indicating p53-medicated DNA repair process. Thus, in addition to the activation of p53 gene expression, IR induces gene mutations of the tumor suppressor p53. These X-ray-associated p53 gene mutation is dominated by the specific G-A transition at the particular purine-rich clusters (AAGG, AAGGG) of the coding region, and these X-ray-specific "footprint" differed from those of UV, PUVA, particle irradiation, as well as other carcinogen.

H 4

TELOMERE LENGTH AND CHROMOSOMAL INSTABILITY IN MAMMALIAN CELLS EXPOSED TO LOW- AND HIGH-LET RADIATIONS.

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Telomeres are specialized nucleoprotein complexes that serve as protective caps of linear eukaryotic chromosomes. The loss of the ends chromosomes due to these un-rejoined DSBs may not be lethal to the cell, but may instead result in the loss of functional telomeres, chromosome fusion, and initiation of breakage/fusion/bridge cycle-induced chromosome instability.
The telomeres also partecipate in process of chromosomal repair, as evidenced by "de novo" synthesis of telomere repeats at DSBs and by the capacity of telomeres to bound the essential components of the DNA repair machinery.
Based on the observation that high-LET radiations efficientely induce chromosome aberrations, we tested whether low energy protons were able to affect telomere structure. Human primary fibroblasts (HFFF2) and mouse embryonic fibroblasts (MEFs) were irradiated with 4 Gy of 31 keV/um of protons at the radiobiology facility at the 7 MV Van de Graaff CN of the INFN-LNL. Experiments with X-rays were also carried out. Cells were fixed after either 24 hrs or 15 days from treatment. Before harvesting, chromosomes were allowed to condense throught 30' incubation with Calyculin-A, an agent able to induce premature chromosome condensation. To evaluate radiation-induced alterations of telomere length, Q-FISH staining was performed on condensed chromosomes and interphase nuclei with fluorescent PNA telomeric probe and telomere size was analysed with TFL-TELO software.
Preliminary results will be presented and discussed.

I 1

CLUSTER EFFECTS WITHIN THE LOCAL EFFECT MODEL

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The Local Effect Model (LEM) has been successfully used in treatment planning for heavy ion therapy with carbon ions at the treatment facility at GSI. Numerous comparisons of the results of LEM with experimental data prove its applicability to a variety of biological endpoints. However, so far, cluster effects of damages at the nanometer scale have not been taken into account.

In line with the main idea of the LEM, we take the yield of single (SSB) and double strand breaks (DSB) from experimental photon data and use a Monte-Carlo method to distribute them onto the DNA. We score clusters of SSBs, where individual SSBs are separated by less than 25 bp as additional DSBs. Assuming that the number of DSBs is a measure for cell lethality, which was experimentally found in many cell lines, we can calculate a modified survival curve for photons, which takes the cluster effects into account. As a consequence of the new approach, the ratio of maximum RBE values to minimum RBEs is increased. This can be understood in terms of a higher radiation effect resulting from the cluster damage at high local doses. We find that the extended LEM including cluster effects reproduces most experimental data better than the original LEM.

This cluster extension enhances the accuracy of the LEM and will improve treatment planning for heavy ions. Additionally, we also find a significant improvement for the modelling of proton data, which will eventually facilitate treatment planning for protons based on LEM.

I 2

FIRST ATTEMPTS AT PREDICTION OF DNA CLUSTERED-LESION YIELDS USING NANODOSIMETRIC DATA

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This work reports on our first attempts for predicting clustered-lesion yields to DNA, on the basis of nanodosimetric information. Such information is available either from Monte Carlo simulations or from experimental measurements using, for example, ion counting nanodosimetry. The latter is a novel method, providing a precise quantification of ionization cluster yields in a gas model of short DNA segments. We applied this method to measure ionization-cluster yields induced by light-ion beams (protons and Helium nuclei) over a wide LET range; in addition, we measured the yields of double-strand breaks and other clustered lesions induced in plasmid DNA, irradiated under the same beam conditions.
We present the preliminary results of our attempts to correlate between the nanodosimetric data and the corresponding radiobiological results, using a simple statistical model of DNA lesion formation. We also provide a comparison, based on the same statistical model, of simulated nanodosimetric data for electrons and published double-strand break yields obtained with the PARTRAC code, which could be an additional validation of our simple model.
We discuss the validity of modeling DNA damage by gas ionizations and the specific advantages and problems arising from this approach.

I 3

INFLUENCE OF DIFFERENT DOSE RATES ON CELL RECOVERY AND RBE AT DIFFERENT SPATIAL POSITIONS DURING PROTRACTED CONFORMAL RADIOTHERAPY.

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Conformal radiotherapy such as rotational irradiation or intensity-modulated radiotherapy (IMRT) concentrates dose in the target volume while spreading the dose to co-irradiated normal tissue over a larger volume receiving a lower dose. The rotational irradiation implicated in these techniques may, however, results in markedly different dose rates on the same isodose curves. Thus, normal tissue near the skin surface will be exposed to a higher dose rate when inside the direct beam and a low dose rate when outside the beam, whereas deep tissue will receive a more homogenous dose rate during the whole irradiation. Since the dose rate influences sublethal damage (SLD) repair occurring during protracted irradiation, this would influence the radiosensitivity and thus the RBE observed at different positions. In order to test the possible magnitude of this effect, we analysed cell survival data obtained previously for V79 hamster cells irradiated in a therapy phantom using rotational irradiation with fast neutrons (14 MeV from the Heidelberg d(0.25)+T neutron generator; dose rate ~ 1.5 cGy/min in dose maximum). The effect of repair on the RBE values observed in different positions at 100%, 55% and 35% isodose levels was modelled using the linear-quadratic formalism with the Lea-Catcheway time factor for simultaneous induction and repair of SLD. Experimental data on repair half times for V79 cells derived from irradiation with different dose rates of 50 kV x-rays will be presented. Experimental RBE values with and without this correction are compared and the implications for protracted irradiation discussed.

I 4

TEST OF THE LOCAL EFFECT MODEL (LEM) USING CLINICAL DATA: TUMOR CONTROL PROBABILITY FOR LUNG TUMORS AFTER TREATMENT WITH CARBON ION BEAMS

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At HIMAC / Chiba, clinical studies for the treatment of lung carcinomas with carbon ion beams were performed, which are particularly suitable for a comparison with the treatment planning approach used within the heavy ion tumor therapy project at GSI Darmstadt. This treatment planning includes a biological optimization, which is based on a biophysical model (the Local Effect Model). As input parameters, the model re-quires information about the sensitivity of the tumor against conventional photon radia-tion. Detailed information, in particular concerning the interindividual variation of ra-diosensitivity, is available for the lung cancer patients.

Predictions of the LEM are in good agreement with the clinical data., and the steeper dose response for carbon ions as compared to photon radiation is reproduced correctly. This steeper increase corresponds to an increasing RBE with increasing dose, which apparently is in contradiction to the systematics observed in general for in-vitro meas-urements. However, this contradiction can be resolved when taking into account the interindividual variation of photon sensitivity. According to the principle of the LEM, and in accordance with experimental findings, the more resistant tumors are expected to show higher RBE values than the more sensitive tumors. Consequently, the range of sensitivity variation after high-LET radiation is significantly reduced compared to pho-ton radiation, finally leading to the higher steepness of the TCP-curve after carbon ion radiation.

I 5

EVIDENCE OF LOW-DOSE HYPER-RADIOSENSITIVITY IN NORMAL CELLS OF CERVIX CANCER PATIENTS?

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We examined the low-dose radiation response of human fibroblasts and keratinocytes using the micronucleus assay. Skin fibroblasts and epidermal keratinocytes derived from 40 cervix cancer patients were studied. After in vitro -irradiation with single doses ranging from 0.05 to 4 Gy, the fraction of binucleated cells with micronuclei was assessed. For each patient, the linear-quadratic model was fitted separately to the low-dose data (from 0.05 to 0.75 Gy) and to the high-dose data above 1 Gy, and the a-coefficients (initial slopes) after both fits compared. The induced repair (IR) model was next fitted over the whole data set (0.05 - 4 Gy), yielding the ratio of initial slopes for the low dose region, a_s, and over the high dose region, a_r . In fits of the IR model, values of a_s higher than a_r (a_s /a_s 3) were found for the fibroblasts of three patients and for the keratinocytes of one patient of the 40 patients studied. Thus, we believe to have observed some evidence of low-dose hypersensitivity in the normal fibroblasts and keratinocytes in our group of cervix cancer patients.

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I 6

ALPHA-HIT, CELLULAR DOSE, CELL TRANSFORMATION AND INACTIVATION PROBABILITY DISTRIBUTIONS OF RADON PROGENIES IN THE BRONCHIAL EPITHELIUM

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Based on published results, deposition of inhaled particles is strongly non-uniform within central airway bifurcations. Thus, the emitted alpha-radiation originating from deposited radon progenies may cause significant bronchial cell damages to the nearby cells at areas where the local deposition densities are high.
The main objective of the current research is to construct a mathematical model which quantifies the radiation burden distribution of the bronchial epithelial cell nuclei (number of hits by alpha particles, specific energy and dose) following inhalation of radon and its progenies, and assesses the resulting biological effects at the cellular level (cell inactivation and transformation probabilities). The FLUENT™ computational fluid dynamics code has been used to determine the deposition patterns in a realistic bronchial airway geometry. The interaction of the alpha particles and the epithelial cells has been analyzed by applying a complex hit probability model (Bronchial Alpha Hit Model). The biological response of the hit cells has been calculated by the Probability-Per-Unit-Track-Length Model which relates the probability of a specific biological effect to the track length of alpha particles as a function of the particles LET. The calculations indicate that transformation probabilities are highest at bronchial carinal ridges, consistent with the deposition pattern.

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L 1

ELUCIDATING RADIATION EFFECTS ON CENTROSOMAL AND CHROMOSOMAL STABILITY IN HUMAN MAMMARY EPITHELIAL CELLS

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The centrosome acts as the major organizer of the microtubule network in many cell types, and participates in a wide variety of cellular processes, notably chromosome segregation. Centrosome abnormalities (CA) can lead to chromosome instability (CIN) in epithelial cells. CA and CIN (especially aneuploidy) have been both correlated to risk and progression of breast cancer. Centrosomal amplification occurs through a number of mechanisms within cancer cells. We have shown that ionizing radiation rapidly induces centrosomal amplification within viable, non-malignant human mammary epithelial cells (HMEC). But while many publications correlate centrosomal amplification, or aberrant centrosomes, to CIN within bulk populations, there are relatively few reported publications directly demonstrating aneuploidy downstream of centrosomal amplification. We hypothesized that the high-frequency of radiation-induced genomic instability (RIGI) might result from radiation-induced CA and subsequent chromosomal stability. By specifically investigating the effect of IR on centrosomal amplification and downstream CIN, this study will relate a biologically relevant breast carcinogen to induction of CA within normal cells.

Can the effect of radiation on centrosome stability be translated into CIN in a quantitative manner? We have used digital imaging and image analysis to evaluate the centrosomes of large numbers of cells. The frequency of CA induced by radiation was linear from 0.1 to 2 Gy in two distinct HMEC lines. Furthermore CA persisted in the progeny of irradiated HMEC. To investigate the direct participation of centrosomal abnormalities in initiating CIN, and not a simple correlation between the two phenotypes, we will expand our analysis of centrosomal abnormalities from population to clonal analyses. We cloned MCF10a HMEC after exposure to X-rays (5-7 days post-irradiation) we observed amplification of the frequency of supernumerary centrosomes and multinucleated progeny. The surviving clones were expanded for centrosomal and chromosomal analysis alternatively; expanded clonal populations were divided for separate centrosomal and chromosomal analysis. Initial experimentation focused on metaphase analysis of clonal populations post-irradiation as it was informative for aneuploidy as well as additional aberrations. Results of these experiments will be presented to answer whether a quantitative relationship exists between centrosomal abnormalities and genomic instability.

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L 2

BYSTANDER RESPONSE IN TK6 CELLS: APOPTOSIS AND DNA DAMAGE INDUCTION

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In the present study we analysed the bystander response induced in non-irradiated TK6 cells by the irradiated conditioned medium (ICM) derived from the same cell line irradiated with 1 Gy of rays. After irradiation the medium was incubated for 6 h, filtered and used to treat non-irradiated TK6 cells. For detection of apoptotic morphology, at least 2000 DAPI stained cells were scored at 24-72 h after ICM incubation. The activity of caspase-3 was measured at the same time-points by a fluorescence assay; moreover, the formation of -H2AX foci in bystander cells was examined as markers of DNA double-strand break formation. A significant increase of apoptosis up to 72 h after ICM incubation was observed in non-irrdiated TK6, as in directly irradiated cells. The ICM derived after 3 cell generations from irradiation retains the ability to induce apoptosis. A significant decrease of apoptosis induction was measured when ICM was added together with the inhibitor of caspase-8; on the contrary no effect was measured adding superoxide dismutase and N-acetylcysteine to the cells. Non-significant increase of -H2AX foci over the control has been observed in TK6 ICM treated. Our data suggest that the bystander signal needs of procaspase 8 activation and does not consist in reactive oxygen species directly generated by irradiation, but derives from the metabolism of irradiated cells. Moreover, the damage induced by the bystander signal does not consist in DNA double-strand breaks.

L 3

EXPERIMENTAL TECHNIQUES FOR STUDYING BYSTANDER EFFECTS IN VITRO BY HIGH AND LOW-LET IONIZING RADIATION.

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Exposure to ionising radiation can induce responses within non-exposed neighbouring or bystander cells. These effects may have important implications on the estimates of risk from low dose or low dose rate exposures of ionizing radiations. It is also unclear whether the bystander effect may lead to an increase or decrease in the overall risk.

The MRC have developed a range of strategies for investigating bystander effects in vitro for both high-LET -particles or low-LET ultrasoft X-rays using either partial shielding (grids, half-shields and slits) or by using a co-culture system where two physically separated populations of cells can be cultured together, allowing one population of cells to be irradiated while the second population remains unirradiated. Although these two populations are not in direct contact, so cannot communicate via direct cell to cell contact, they do share the same medium allowing communications by media borne factors. The various experimental systems will be described along with results from a number of experiments demonstrating a bystander effect for a range of cell types and biological end points and indicating an important role for media mediated effects. These include protein expression in primary rat trachea epithelial cells and human AG1522 cells, chromosomal instability in haemopoietic stem cells and transformation in CGL1 cells.

L 4

KEEPING UP WITH THE NEIGHBOURS - MEASURING THE BYSTANDER RESPONSE

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The Bystander response is now a well-established phenomenon. The biological effects of alpha particles, namely Radon gas, are of particular interest since they are the dominant natural source of environmental ionising radiation exposure for the general population. Traversed cells can experience a substantial amount of DNA damage caused by the deposition of a large amount of energy in a narrow traversal path. Induction of CDKN1A, a cyclin dependent kinase inhibitor which is transcriptionally activated by p53, is an integral part of cell growth arrest and has been shown to be an effective reporter system for measuring both initial DNA damage caused by irradiation and also a bystander response in neighbouring unirradiated cells.

The aim of this study was to determine how CDKN1A expression is altered after irradiation and the means of communication (medium-borne or gap junction) by using a co-culture system and artificial irradiation zones. Recently use of a nuclear track etch detector has allowed us to precisely locate of each traversal and thus changes in CDKN1A levels in bystander cells can be assessed with distance from the irradiation edge.

L 5

GAMMA RAY-INDUCED BYSTANDER EFFECT IN TUMOUR GLIOBLASTOMA CELLS: A SPECIFIC STUDY ON CELL SURVIVAL, CYTOKINE RELEASE AND CYTOKINE RECEPTORS.

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Recent experimental evidence has challenged the paradigm according to which the radiation traversal through the nucleus of a cell is a prerequisite to produce genetic changes or biological responses. Thus, unexposed cells in the vicinity of directly irradiated cells or recipient cells of medium from irradiated cultures can also be affected by radiation exposure.
The aim of the present study was to evaluate, by means of the medium transfer technique, whether the medium from irradiated T98G cells affects the clonogenic survival of non-irradiated T98G cells, and whether cytokines and their receptors may play a role in the bystander effect after gamma irradiation of T98G cells in vitro. In fact the cell-specificity in inducing the bystander effect and in receiving the secreted signals that has been described, suggests that not only the ability of releasing the cytokines but also the receptor profiles are likely to modulate the cell responses and the final outcome. The dose- and time-dependence of the cytokine release into the medium, quantified with ELISA, showed that radiation causes alteration in the release of both IL-8 and TGF from exposed cells in a dose-independent but time-dependent manner. The relative receptor expression was also alterated in unexposed cells incubated with conditioned medium.
Acknowledgment: this work was carried out within the European master of radiation biology program.

L 7

COMBINED ACTION OF VERY LOW DOSE-RATE GAMMA-RADIATION AND RADIOACTIVE STRONTIUM ON THE YIELD OF CYTOGENETIC DAMAGE IN MICE IN VIVO

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Our previous studies of the effect of low doses of ionizing radiation (IR) showed that both acute and chronic irradiation induce the adaptive response (AR) and genetic instability in the F1 generation of mice. Adaptive response makes itself evident as a decrease in the damaging effect of high doses of radiation after preliminary irradiation of cells with low doses (5-20 cGy). In the last few years the problem of the effect of chronic low-intensity IR at low doses on living organisms has acquired a particular value in view of the possible combined action of different environmental factors, in particular, heavy metal ions. The goal of the work was to determine whether the combined action of chronic low-intensity IR and radioactive Sr induces adaptive response and genetic instability in bone marrow cells of mice in vivo and to study the dependence of cytogenetic damage on the doses used. CBA/lac mice were irradiated using a 137Cs source (0.17 cGy/day) for 40, 120, and 210 days, which corresponds to doses of 6.8, 20.4, and 35.7 cGy. Acute irradiation (1.5 Gy) was produced using the 137Cs source (28.2 Gy/h). SrCl2 at a concentration of 70 mg/l (calculated for ions) was given to animals with drinking water throughout the irradiation period. Cytogenetic mouse bone marrow preparations were prepared by the standard method, and the frequency of polychromatophil erythrocytes (PCE) with micronuclei was determined. For each mouse 2000 PCE were analyzed. It was found that the combined effect of chronic low-intensity radiation and radioactive Sr (1) does not affect the yield of cytogenetic damage over a period of 40 days, and only after the 210-day exposure an insignificant increase in the damage was observed; (2) induces AR after a 210-day exposure; and (3) induces genetic instability in the F1 generation obtained from males irradiated for 210 days.

L 8

THE EFFECTS OF ACUTE AND CHRONIC IRRADIATION IN 1 GY DOSE ON ENDOTHELIUM- AND NO-DEPENDENT VASCULAR REACTIVITY

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The epidemiological and clinilal evidences indicate the increased incidence of cardiovascular diseases among population of contaminated with radionuclides areas and liquidators of the consequences on Chernobyl nuclear power station. It may be assosiated with postradiational changes in metabolism of nitric oxide (NO) - one of the most important regulator in cardiovascular system. Endothelium- and NO-dependent relaxation of aortic segments and basal coronary flow and response of coronary vessels to exogenous NO in the Langendorff-perfused rat hearts were examined on the 3rd, 10th, 30th and 90th days following 1 Gy whole body irradiation with different dose rate. NO-mediated elevation of coronary flow and increased aortic endothelium-dependent vasodilation were found at the early stage after acute irradiation (137Cs, 9x10-4 Gy/s), while vascular reactivity to exogenous NO was not changed. Chronic irradiation (137Cs, 2.3x10-7 Gy/s) significantly impaired endothelium-dependent relaxation within whole experimental period and decreased NO component of basal coronary flow at the 3rd, 10th and 90th day. It was associated with attenuated reactivity to NO-donor in aorta one month after irradiation and in the coronary vessels - shortly after irradiation. In the delayed period endothelial dysfunction and the diminution of NO-dependent coronary flow were mediated by selective impairment of NO synthesis/release. Decreased survival rate of the lethally-irradiated N nitro-L-arginine methyl ester - treated animals revealed radiosensitizing properties of NO-synthase inhibition, while -tocopherol treatment was radioprotective. The data obtained indicate the involvement of NO in the alterations of vascular reactivity depending on the dose rate and on the interval after irradiation.

L 9

BYSTANDER EFFECTS WITHIN A STATE VECTOR MODEL FOR NEOPLASTIC TRANSFORMATION

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A State Vector Model (SVM) for chromosome aberrations and neoplastic transformation has been adapted to describe detrimental and protective bystander effects. The model describes initiation (formation of translocations) and promotion (clonal expansion and loss of contact inhibition of initiated cells). Additional terms either in the initiation model or in the rate of clonal expansion describe detrimental bystander effects for chromosome aberrations as reported in the scientific literature. In the present study the SVM with bystander effects is tested on suitable data sets (Nagasawa and Little, Mutat. Res. 508(1-2), 121-129, 2002). The model is also extended with a pathway for apoptosis in addition to its dose-rate dependent cell-killing term. This allowed a description of in vitro data that show protective effects of low doses of low-LET radiation for neoplastic transformation, which has been discovered in recent years. A suitable data set will be used to test the model (Redpath et al., Radiat. Res. 156(6), 700-707, 2001). Both effects are included in a dose-dependent way with the effects being strongest at low doses. In the model apoptosis can eliminate cells that have chromosome damage and those that are initiated. In addition to the simulation of non-linear effects, a classical data set for neoplastic transformation after -particle irradiation (Miller et al., Radiat. Res. 142(1), 54-60, 1995) is used to show that the model without bystander features can also describe LNT-like dose-responses.

L 10

THE EFFECTS OF CHRONIC ENVIRONMENTAL RADIATION ON AQUATIC ORGANISMS WITHIN THE CHERNOBYL EXCLUSION ZONE

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The rate of chromosome aberrations in cells of freshwater snail (Lymnaea stagnalis L.) embryos and in the apical meristem of roots of the higher aquatic plant common reed (Phragmites australis (Cav.) Trin. ex. Steud.) and arrowhead (Sagittaria saggitifolia L.) has been studied. The samples has taken in different seasons of 1999-2004 in reservoirs within the inner (10-km) exclusion zone of the Chernobyl NPP - Azbuchin Lake, Dalekoye-1 Lake, Glubokoye Lake, cooling pond, Yanovsky Creek, Uzh River and Pripyat River. The chromosome aberration rate was registered by anaphase method. The results of the analyses compared to the data received for hydrobionts from Goloseevo lakes located within Kiev City territory. The absorbed dose rate for hydrobionts, living within littoral zone of the researched water objects, due to external irradiation and radionuclides incorporated in tissue was in a range from 2.5E-04 to 3.4 Gy year-1. The highest value was found for hydrobionts from lakes within the embankment territory on the left-bank flood plain of the Pripyat River (Dalekoye-1 Lake and Glubokoye Lake), the lowest - for specimens from the running water objects (Uzh River and Pripyat River). The molluscs from Dalekoye-1 Lake and Glubokoye Lake were characterised by the maximal rate of chromosome aberration - about 20-25 %, that in 10 times exceeds a level spontaneous mutagenesis for hydrobionts. A little bit less rate is registered for snails from Azbuchin Lake and Yanovsky Creek. The chromosome aberration rate of hydrobionts from Goloseevo lakes on average was about 1.5 %, and the maximal rate did not exceed 2.5 %. The maximal aberration rate in roots of higher aquatic plants (7.8 %) has registered in Glubokoye Lake; in plants of Goloseevo lakes this value was about 1.8 %. The cytogenetic research of aquatic biota within the exclusion zone convinces that the organisation of regular genetic monitoring of the contaminated territories is the important measure, extremely necessary for understanding and forecasting of negative remote consequences of long-term irradiation.

M 1

SINGLE PROTON IRRADIATION OF LIVING CELLS AT THE NEW LUND SUB-MICRON BEAM LINE

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Since a few years ago, biological applications have become very important within IBA. The CELLION project is directed towards the studies on cellular response to targeted single ions.
Currently, in order to estimate low-dose radiation risk a Linear No Threshold (LNT) model is assumed. The final aim of the project is to obtain the necessary data which allow us to understand the real effects of the low-dose radiation. In order to achieve this, a new sub-micron beam line has been adapted at the Lund Nuclear Probe. Such a system is capable to control single ions to irradiate individual and living cells.
The development of single ion hit facilities using a sub-micron beam line is done in several steps. The current is limited by slits to approximately 1000 ions per second. A fast beam deflecting system combined with an after target particle detector is used to prevent secondary hits; i.e., to limit the dose applied. The beam is extracted to the atmospheric environment using a 200nm Si3N4 vacuum window.
A microscope connected to a CCD camera with specific software is used to locate the cells. A program for cell recognition and location has been developed at the Lund facility. It provides the coordinates of the centre of the cell. Since the procedure is not completely optimised, the main purpose is to locate the cell without distinguishing between cytoplasm and nucleus.
Preliminary tests using an etch track film CR39 has proved a proper targeting accuracy.

M 2

STUK BROAD/NARROW BEAM ALPHA-PARTICLE IRRADIATION FACILITY

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238Pu based broad/narrow beam a-particle irradiation facility is designed for bystander effect/genomic instability experiments. a particle 238Pu source housed in a stainless steel tube flushed with He gas. Source activity is 1.1x109 Bq (30 mCu). High activity is essential for upgrade of the facility to narrow beam mode. Maximal a-particle energy at the source surface is 5.5 MeV. A precise photo shutter above the source regulates irradiation times. This allows a high energy and dose rate to be obtained with the source at some distance from the window. The source window is made from 2 um thick mylar with a circular diameter of 30 mm. A thumb-wheel allows us adjusting the source position and therefore changing energy/LET of the particles at the exit window. The facility is used for irradiations of cell cultures and 3D tissue samples at a single or multiple spot(s) with a time-averaged calculated number of particles, when precision targeting is not required or for broad beam experiments. We plan to upgrade the irradiator in 2005-2006 with a removable collimator system and X-Y motorised stage allowing precise micron range patterned irradiation, positioning and repositioning of biological samples. The main part of the collimator will be two layers of a metal foil (10-20 mm diameter in frame of 35 mm diameter and 0.2-1 mm thick) with a central aperture of 1 µm in diameter. Collimator will be manufactured by using laser drilling technique. We plan to achieve a 10-20 um spot size for narrow beam mode of operation.

M 3

DEVELOPMENT OF A NANOTECHNOLOGY BASED LOW LET MULTI-MICROBEAM ARRAY SINGLE CELL IRRADIATION SYSTEM

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Advancements in the fields of radiation therapy and radiation protection are hindered by our lack of a thorough understanding of molecular events that underlie the radiation response of cells. Single cell irradiation (SCI) is a state of the art research technique that can enable researchers to improve this understanding[1]. Recently, there has been increased interest in the radiation research community in SCI systems that use a low LET microbeam and are accessible to average research laboratories[2]. We have proposed to develop a novel portable single cell irradiation device enabled by a carbon nanotube (CNT) based field emission electron source. CNTs intrinsically produce collimated electron beams under an applied electric field and are ideal as an electron source of ultra high temporal and spatial resolution. The proposed CNT SCI device is expected to have the following features: a) the size of a Petri dish (excluding the power supply and control system), thus can be made available to average research labs; b) single cell irradiation under the observation of a reflective microscope; c) a multi-microbeam array consisting of a large number of beams that can be individually turned on or off; d) microbeams can be either continuous or pulsed with a frequency of a micro-second; e) electron beam energy between 20-60 keV; and f) an microbeam size expected to be below 10 microns. Our research plan is to first develop a prototype single beam device according to initial specification; secondly, to conduct proof of concept cellular irradiation research; and thirdly, to develop a prototype multi-beam SCI system. Together with recent technological advances in biosensors and cellular imaging, the proposed technology will enable novel research at the cellular and subcellular levels, and at the time scale of microseconds.

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M 4

DEVELOPMENT OF A SINGLE ION HIT FACILITY AT THE PIERRE SÜE LABORATORY: A COLLIMATED MICROBEAM TO STUDY ENVIRONMENTAL RADIOLOGICAL EFFECTS ON TARGETED LIVING CELLS

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A single ion hit facility is being developed at the Pierre Süe Laboratory (LPS) since one year. The setup will be dedicated to the study of ionising radiation effects on living cells which will complete actual researches conducted on uranium chemical toxicity on renal and osteoblastic cells. The study of the response to an exposure to alpha particles will permit to distinguish radiological, as alpha emitter, and chemical, as heavy metal, toxicities of uranium, with a special emphasis on the bystander effect at low doses.

Designed and installed on the LPS Nuclear microprobe, up to now dedicated to ion beam microanalysis, this setup will enable to deliver an exact number of light ions (protons or alpha particles), accelerated by a single stage 3,75MV Van de Graaff accelerator. An "in air" vertical beam permits to irradiate cells in conditions compatible with cell culture techniques. Furthermore, cellular monolayers will be kept in controlled conditions of temperature and atmosphere during and after experiments in order to diminish their stress. The beam is collimated with a 1µm-diameter bore glass capillary to target pre-selected cells. Motorization of the collimator with piezoelectric actuators should enable irradiating cells as fast as 100/s with an accuracy better than 1µm and without moving the sample, thus avoiding mechanical stress. An automated epifluorescence microscope equipped with a cooled CCD camera is mounted on an antivibration table to allow pre- and post-irradiation cells observation. To be able to shoot a cell with a single ion, a high sensitive charged particle detector inducing the lowest hit precision degradation is required. A 3µm-thick silicon surface barrier detector has been tested for alpha particle counting with 100% efficiency.

M 5

THE FOCUSED HEAVY ION MICROBEAM FACILITY AT GSI FOR TARGETED IRRADIATION BIOLOGICAL OF CELLS

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Since the single hit technique was developed at GSI in 1987 for a focused ion microprobe, it was clear that compared to collimated microbeam facilities, it should allow to shoot single ions into living cells with higher targeting accuracy and a better defined LET.

Since July 2003 essentially all parts of a biological single hit facility are ready and added to the GSI heavy ion microprobe. It will be described in detail, especially what is different from facilities using a collimated microbeam. Some experimental results will be described which show its present performance and the performance which can be expected in the future.

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M 6

A FAST ONLINE HIT VERIFICATION FOR THE SINGLE ION HIT SYSTEM AT GSI

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For a single ion hit facility built to irradiate specific targets inside biological cells it is necessary to prove that the position where ions hit is the position of aimed targets, as the ion hits usually cannot be seen. The ability to hit biological targets is traditionally tested indirectly by aiming at and hitting pre-etched tracks in a nuclear track detector, or directly by making the ion tracks inside cells visible by a stain coupled to special proteins produced in response to ion hits. However, both methods are time consuming and the hit verification comes out after the experiment instead of before targets irradiation, which means errors in the experiment can no longer be corrected. Therefore, we developed a fast online hit verification method that measures the targeting accuracy of the single ion hit facility electronically with a spatial resolution of 2?m before cell irradiation takes place.

M 7

THE PTB MICROBEAM: A VERSATILE INSTRUMENT FOR RADIOBIOLOGICAL RESEARCH.

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Since 2002, the PTB microbeam is routinely used by different collaborators from radiobiological research for the irradiation of living cells. An important feature of the PTB facility is the wide energy range available for protons (up to 20 MeV) and alpha particles (up to 25 MeV), leading to a LET-range of 3 - 200 keV/µm. The beam diameter is approx. 2 µm (FWHM), achieved by focussing, causing essentially no degradation of the energy width and no scattered particles on the specimen. In 2004, an electrostatic scanning device was added to the facility which allows targeting of each cell within a few milliseconds. This and other improvements led to an increase in the experimental speed of the system from 1000 cells per hour to a maximum of 50,000 cells per hour including all experimental steps, such as scanning the dish and cell recognition procedures.
To improve the versatility of the facility, a module for automatic quantification of immunocytochemical staining was implemented. This allows the analysis of protein activation including the positional information of the irradiation. Thus, the signal of irradiated and unirradiated cells on the same dish can be measured separately and the signal of bystander cells could, for instance, be correlated to the distance from the next irradiated cell. The module accomplishes the effective removal of artefacts and an appropriate image enhancement and guarantees a quick and unbiased protein quantification.
The properties of the PTB microbeam facility are presented and examples of results from biological experiments are shown.

M 9

CRACOW SINGLE ION HIT FACILITY FOR CELL IRRADIATION.

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Last years the Cracow ion microprobe has found its new application as a single ion hit facility (SIHF), allowing precise irradiations of living cells by a controlled number of ions. The instrument allows investigating a wide spectra of tasks, such as adaptive response, bystander effect, inverse dose-rate effect, low-dose hypersensitivity etc.
This work presents the principles of construction and operation of the SIHF based on the Cracow microprobe. In our study we discuss some of the crucial features of optical, positioning and blanking systems including a self-developed software responsible for a semi-automatic cells recognition, for precise postioning of cells and for controlling of the irradiation process. We also show some tests carried out to determine the efficiency of the whole system and of its segments. In addition, we present the results of our first irradiation measurements performed with living cells.
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M 10

DEVELOPMENT OF A GOLD GRID PATTERNED MYLAR FOIL AS CELL SUBSTRATE FOR SINGLE-CELL SINGLE-ION IRRADIATION AT INFN-LNL MICROBEAM FACILITY

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A single-cell single-ion microbeam apparatus allows performing a deterministic irradiation in terms of radiation quality (ion type and energy), defined target (a set of cells among a greater population or a specific sub-cell site) and defined dose (number of ions per cell target). In such a way the induced biological effect can be strictly correlated with irradiation parameters. Studying the biological response of irradiated and unirradiated (bystander) cells requires to follow the history of individual irradiated and bystander cells in the same population and to process the two sub-populations separately.
At INFN-LNL single-ion microbeam facility (Gerardi et al., Rad. Res. 164 (2005) 586) cell recognition is performed by a phase contrast optical microscope without using any cell staining or UV light. A special Petri dish has been designed to keep cells in humid and sterile conditions during irradiation. It consists of a 20 μm thick cell chamber, where the base and the cover are mylar foils.
In order to have a fixed reference system for the seeded cells in all the phases of the irradiation protocol, it has been devised a gold grid pattern on the mylar foil used as cell substrate. The patterned mylar has been developed at Angstrom Laboratory, Uppsala (Sweden), in the framework of CELLION project by mounting a slightly stretched foil in a frame that remains all through evaporation, spinning, microlithography and gold etching. Tests have been carried out at the INFN-LNL Radiobiology Laboratory and microbeam facility. Preliminary results will be presented and discussed.

M 11

MICROSCOPE-MOUNTED TRANSPARENT CHARGED PARTICLE COUNTER FOR MICROBEAM APPLICATIONS.

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Single-ion microbeam systems that have been developed in the last few years allow the irradiation of small structures such as the nuclei of cultured cells using a beam of energetic ions produced in an accelerator and then confined to a diameter on the order of a micron. A typical experiment is to allow one or a few ions to pass through each target that has been located and placed in the path of the beam. One of the challenges in constructing such a system is to detect the particles while simultaneously positioning the targets using video-microscopic observation.
A counter has been constructed for use in detecting ions that have passed through a sample being irradiated in a charged particle microbeam. It is mounted on the objective lens of a microscope so that the sample can be observed and positioned by an integrated video-analysis and microscope stage controller system at the same time that the arriving particles are being counted. The counter is filled with gas, normally P-10, at atmospheric pressure that is confined to the counter with an optically clear window. The counter has a thin electrode centered in a field-shaping helical electrode that produces a high gas gain, making it suitable for detecting protons and other low-LET ions, as well as soft X rays.

M 12

MICROBEAM IRRADIATION WITH 2.1 MEV ALPHA PARTICLES ACTIVATES NUCLEAR FACTOR B DEPENDENT GENE EXPRESSION IN HUMAN CELLS

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Cellular stress protection responses lead to increased transcription of several genes via modulation of transcription factors. Activation of the Nuclear Factor B (NF- B) pathway as a possible anti-apoptotic route represents such an important cellular stress response. A screening assay for detection of NF- B-dependent gene activation using the destabilized variant of Enhanced Green Fluorescent Protein (d2EGFP) as reporter protein had been developed. This screening assay consists of Human Embryonic Kidney (HEK/293) Cells stably transfected with a receptor-reporter-construct carrying d2EGFP under the control of the NF- B response element. Clones positive for Tumor Necrosis Factor (TNF-a) inducible d2EGFP expression were selected as cellular reporters. Radiation was performed either with X-rays (150 kV, 19 mA) at DLR, Cologne, or with 2.1 MeV particles (LET ~160 keV/µm) at PTB, Braunschweig. After radiation the following biological endpoints were determined (i) cell survival via the colony forming ability test, (ii) time-dependent activation of NF- B dependent d2EGFP gene expression using flow cytometry. Cellular response to TNF-a was much more pronounced (up to 90 % of EGFP+ cells) than to X-radiation. Radiation experiments using low-LET ionizing radiation (150 kV X-rays) at 0 °C show an only slight but yet not significant increase of NF- B dependent d2EGFP fluorescence after 5 Gy. For X-irradiation applied at 37 °C, a significant dose-dependent increase in d2EGFP fluorescence can be verified. This may either reflect the dependence of NF- B activation on free floating receptors or on DNA repair processes actively running already during irradiation. After exposure with 1 to 10 nuclear hits of 2.1 MeV particles at 37 °C, d2EGFP fluorescence can already be seen 12 hours after exposure, with a maximum after 36 h. After exposure of HEK cells with 5 nuclear hits, when maximal NF- B activation is achieved, about 60 to 70 per cent of the irradiated cells survived. The reported experiments have clearly shown, that the NF- B pathway is inducible by as less as 1 nuclear hits of particles (2.1 MeV, LET ~160 keV/µm) which result in a nuclear dose of about 0.25 Gy (maximal NF- B activation at 5 nuclear hits corresponds to 1.2 Gy). As activation of the NF- B pathway is supposed to play a role in the negative regulation of apoptosis, survival of cells with DNA damage might be favoured especially after low doses of densely ionising radiation.

M 13

BIOLOGICAL VALIDATION OF THE CENBG ION-MICROBEAM USING NEW TRANSGENIC KERATINOCYTE CELL LINES EXPRESSING GFP-TAGGED PROT

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To study the molecular basis of cellular response such as repair, cell cycle arrest and apoptosis, microbeam can be used to generate localized ionizing radiation (IR) induced-damage within restricted regions of the nuclei. Based upon ion-microbeam techniques developed at CENBG for targeted irradiation of individual cells, in full control mode (down to the ultimate dose of one alpha particle per cell) and upon transgenic cellular models, we are studying the metabolic responses after low dose of in vitro radiation exposure of sub-cellular targets. The lesions can be visualized indirectly and rapidly in the form of IR-induced foci using immunocytochemical detection or GFP-tagged proteins. So, we established by transfection a human keratinocyte cell line (HaCaT) expressing the histone H2B-GFP tagged protein and in combination with immunocytochemical techniques using antibody targeted against the specific phosphorylated form of histone H2AX (g-H2AX), we analyzed the DNA double-strand breaks induced by alpha particles. Using confocal microscopy, H2B-GFP allowing high-resolution imaging of both mitotic chromosomes, interphase chromatin and chromatin alterations (apoptosis) and g-H2AX staining, we have shown a correlation between the DNA double-strand breaks observed and the number of incident alpha particles. These prelimiray data demonstrate that the CENBG microbeam line setup is a efficient tool to study the molecular pathways involved in the response to IR and we plan to : 1) define biological indicators as a function of dose; 2) validate in silico biological models of IR induced-damage (Monte Carlo simulation).

M 14

SINGLE CELL IRRADIATION SYSTEM WITH MICRO FOCUS X-RAY SOURCE

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A single cell irradiation system with a micro focus X-ray source was developed to research cell damages such as chromosome aberrations and mutants. The system was composed of a micro focus X-ray tube, an X-ray guide tube, an X-ray detector for fluorescent X-ray analysis and an optical microscope. The intensity of an X-ray microbeam was measured and its diameter was 14 ?m [FWHM]. The dose rate for cells was obtained from the photon-electron transport calculation and the maximum dose rate was estimated to be about 0.1 Gy/s.
The single-cell irradiations were preliminarily performed using the yeast cells. The budding yeast Saccharomyces cerevisiae was irradiated with the micro X-ray beam irradiation system, and the maximum dose for the samples was 120 Gy. After the X-ray irradiation, the irradiated yeast cells were incubated at room temperature, and the time-lapse images of the irradiated cells were collected during incubation. After incubation for 20 hours, the growth and division of the cells was hardly observed. This result shows that the X-ray beam was successfully delivered to the targeted cells, which had the lethal dose of X-rays.

M 15

RADIATION-INDUCED RESPONSES IN MAMMALIAN CELLS IRRADIATED WITH SYNCHROTRON X-RAY MICROBEAM

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We have developed an X-ray microbeam irradiation system using synchrotron radiation, by which we can recognize cells individually and irradiate one by one with desired dose of monochromatic X-rays. Developed system was installed at BL-27B in the Photon Factory, KEK (Tsukuba, Japan).
Human fibroblast cells (NB1-RGB) were individually irradiated with X-ray microbeam, and fixed and stained by g-H2AX antibody. The slit system installed just below the sample stage enable to change the size of the beam easily and the minimum size is 5 micrometer square. We irradiated the cells with two different beam-sizes, 5 and 10 micrometer square. All the irradiated cells could be found at the revisited position, and could be distinguished from surrounding unirradited cells by their high yield of fluorescence of g-H2AX. Most fluorescent foci were observed in localized area in cell nuclei, the sizes of which were almost the same as the beam size. Different sizes of the stained area can be easily recognized between cells irradiated 5-micrometer beam and those irradiated with 10-micrometer beam. Dose dependence of g-H2AX induction was also clearly observed.
Survival study, which needs to irradiate many cells individually and sequentially with the microbeam, has also been done using Chinese hamster V79 cells. The result clearly indicates that the cell nucleus is the target organelle in deciding the cell killing effect.

N 1

ANALYSIS OF IONISING RADIATION INDUCED FOCI IN HUMAN G0 LYMPHOCYTES CULTURED IN 1G AND IN MODELED MICROGRAVITY

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Double strand breaks (DSBs) are the most severe lesion induced by ionising radiation (IR). Histone H2AX is rapidly phosphorylated (-H2AX) by ATM (Ataxia Telengiectasia Mutated) kinase in the chromatin surrounding the DSBs. Approximately 1% of the H2AX becomes phosphorylated per Gy of IR, reaching the maximum 1 min to 1 hour after irradiation. g-H2AX is involved in the recruitment of many proteins of DNA repair to the sites of the DSBs, forming the ionising radiation induced foci (IRIF). Analysis of g-H2AX foci was carried out in human G0 lymphocytes irradiated with X rays and cultured in modeled microgravity (MMG) or in normal gravity (1g) after irradiation. At 30', 2h, 6h and 24h from irradiation, the cells were stained for immunofluorescence with anti H2AX antibody. IRIF formation was higher at 30' and 2h from irradiation and decreased at 6 and 24 hours, both in 1g and MMG. The number of foci-positive cells was higher in MMG at 6h and 24h from irradiation. This is in agreement with an impairment of DNA repair process when the cells were incubated in MMG rather than 1g after irradiation, as already suggested by the higher HPRT mutant frequency measured in MMG (Mognato and Celotti, 2005). Immunofluorescence and immunoblotting of the phosphorylated ATM and NBS1 (Nijmegen Breakage Syndrome) proteins are under investigation to assess possible alteration of DNA damage signalling in modeled microgravity. Preliminary results show that co-localization of NBS1 in the -H2AX foci is affected by the low gravity condition.

N 2

SOLID-STATE MICRODOSIMETRIC SYSTEM FOR A SATELLITE SCHEDULED FOR LAUNCH IN 2006

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Purpose: In May of this year, our group presented to the 15th IAA Humans in Space Symposium a system being designed and built for inclusion in a satellite (MidSTAR) to be launched in 2006. The purpose of the system is to obtain microdosimetric data in orbit as a proof of concept of the technology. The system will be under the control of the satellite command center at the U. S. Naval Academy in Annapolis, Maryland with data periodically transferred to that center. The system has also received ranking by the Navy Space Experiment Review Board (SERB) as a candidate for possible inclusion on the International Space Station. The system uses custom integrated circuits as detectors that can be embedded in different materials such as polyethylene, spacesuit fabric, and candidate shielding material to obtain microdosimetric spectra in real time. The detectors are rugged, have low power consumption, and are computer controlled, so they are ideally suited for space applications. The system for the MidSTAR spacecraft has been constructed and is undergoing tests. It consists of three sensors, one on the exterior, one in the interior and one encased in polyethylene. We look forward to an opportunity to review this research and its application with the microdosimety research community.

N 3

HUMAN EXPOSURE TO SPACE RADIATION: ROLE OF PRIMARY AND SECONDARY PARTICLES.

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Human exposure to space radiation implies two kinds of risk, both stochastic and deterministic. Shielding optimization therefore represents a crucial goal for long-term missions, especially in deep space.
In this context, the use of radiation transport codes coupled with anthropomorphic phantoms allows to simulate typical radiation exposures for astronauts behind different shielding, and to calculate doses to different organs.
In this work we used the FLUKA Monte Carlo code and two phantoms, a mathematical model and a voxel model, taking the GCR spectra from the model of Badhwar and O' Neill (1996). The time integral spectral proton fluence of the August 1972 Solar Particle Event was represented by an exponential function. For each shield thickness, besides total doses we calculated separately the contributions from primary and secondary particles for different organs and tissues. More specifically, we calculated fluences, absorbed doses, dose equivalents and a form of "biological dose", defined on the basis of initial (clustered) DNA damage.
As expected, the SPE doses dramatically decreased with increasing shielding and doses in internal organs were lower than in skin. The contribution of secondary particles to SPE doses was almost negligible; however it is of note that, at high shielding (20 g/cm2), most of the secondaries are neutrons.
GCR organ doses remained roughly constant with increasing Al shielding. In contrast to SPEs, for GCR secondary particles accounted for a significant fraction of the total dose.

N 4

LINEAL ENERGY AS A FUNCTION OF SITE SIZE FOR HZE RADIATION

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For most radiations, f(y) is a slowly varying function of the site size. However, for the high z high energy (HZE) particles found in space, a significant fraction of all events are produced by delta rays only, and this fraction depends on the site size. Delta rays produced by HZE particles have relatively long range and deposit some energy in sites that are far from the primary ion track. For a uniform radiation field and fixed site size, an increase in particle energy increases the fraction of events which are produced by delta ray interactions alone. Furthermore, the events produced when the primary ion crosses the site become smaller as the site size decreases or the ion energy increases because the delta rays carry a larger fraction of the energy out of the site. Thus, the shapes of two spectra, representing two different site sizes, contain information about the energy of the primary particles. Monte Carlo simulation of energy deposition in a uniform field of charged particles is being used to determine the expected differences in the spectrum as a function of site size and particle energy. The results of simulations are being used to design sets of detectors which can be used to determine the energy and charge of cosmic ray particles in space. Preliminary results indicate that comparison of a 1 micrometer diameter site with one on the order of 10 nm diameter may be the most effective for determining the average energy of the primary ions.

P 1

RELATION BETWEEN TUMOR GROWTH RATES AND BIOLOGICAL EFFECTIVENESS OF CARBON IONS.

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Clinical trials indicate that the RBE value of high LET radiation is large for slow-growing tumors. Using 11 transplantable murine tumors with different growth rates for each, we here investigated and compared RBE values of 290 MeV/u carbon ions. NFSa fibrosarcoma spontaneously arisen in a C3H mouse and other radiation-induced tumors were transplanted in hind legs, and irradiated with either gamma rays or carbon ions (74 keV/micrometer). Tumor growth delay time and specific growth delay were calculated from growth curves, and used to obtain isoeffect doses. Time for a tumor to reach 5 times initial volume for unirradiated control ranged from 3 to 10.3 days. RBE values of carbon ions ranged from 2.1 to 3.4. It is conclude that the tumor growth rate is less important than anticipated as an EBE determinant of carbon-ion radiation.

P 2

TOWARDS BIOLOGY-ORIENTED TREATMENT PLANNING IN HADRONTHERAPY

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Simplified physical model has been used to link the results of analyses based on the probabilistic two-stage radiobiological model with the issues of interest in hadrontherapy treatment planning. The energy-loss, its straggling, and the attenuation of the primary beam are represented in a simplified way, based on semi-phenomenological parameterizations and SRIM calculations. The biological module takes into account, then, the probabilities of individual tracks to form severe damages to chromosomal DNA, and the success probabilities of the subsequent repair processes. Estimated survival for V79 and CHO cells along the penetration depth of carbon ions will be presented, showing good agreement with experimental data.

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P 3

EFFECTS OF GLYCINE BETAINE ON BONE MARROW DEATH AND INTESTINAL DAMAGE BY GAMMA-RAYS AND CARBON IONS

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We previously reported that glycine betaine reduced the chromosome aberrations caused by either g-rays or carbon ions. In this study, we investigated the effects of glycine betaine on bone marrow death and intestinal damage by g-rays or carbon ions. C3H/He female mice, aged 14 weeks, received an i.p.-injection of glycine betaine at 15 min before whole-body irradiation with g-rays or 50 keV/µm carbon ions. The irradiated mice were observed to determine the mortality for 30 days after exposure. Also, the mice were killed at 3.5 days after the exposure to determine the intestinal damage. The jejunum was fixed in formalin and then stained with Hematoxylin and Eosin stain. The numbers of crypts per transverse circumference were counted using a microscope. For the bone marrow death, glycine betaine significantly ($p < 0.05$) increased the percent survival for both radiations. For the intestinal damage, glycine betaine significantly ($p < 0.05$) increased the crypt survival for g-rays, but not for carbon ions. The difference of the protective effects on carbon ions-induced bone marrow death and intestinal damage may be related to the difference in the mechanism of radiation damage in both tissues. In generally, an essential feature of the design of successful radioprotectors in tumor radiotherapy is that they must be hydrophilic. Lipophilic radioprotectors don't show the differential uptake between normal tissues and tumors. Glycine betaine is hydrophilic, might be a potential protector against normal tissue damage as a side effect in radiotherapy.

P 4

PRELIMINARY DATA ON DNA DAMAGE AND BIODISTRIBUTION BY RE IN "IN VITRO" AND "IN VIVO" SYSTEMS

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The aim of the experiment SCINTIRAD is to determine the radio-response of 188Re in in vitro cells and the biodistribution in different organs of in vivo mice and subsequently the therapeutic effect on liver tumors induced in mice inoculated with M5076 murine fibrosrcoma cells.
Both the and - emissions of 188Re have been spoiled in the experiments. In particular, it has been evaluated the capability of the - component (2.12 MeV) to induce inhibition of cell growth and cell death in a panel of human and murine tumor cell lines exposed for 48-72 hours to different acivities of 188Re. The same endpoints, have ben also evaluated after irradiation with 5-10 Gy of X-rays.
A YAP camera and an appropriate software have been developed and improved for imaging of small animals (spatial resolution of 1mm, 4x4 cm field). Though low, the component of 188Re (E=155 keV) has been spoiled to perform scintigraphy of C57/Bl mice inoculated with 188Re conjugated with Hyaluronic acid, a polimer that preferentially accumulates in liver.
The preliminary results so far obtained suggest that radiopharmacs containing 88Re and HA may represent useful tools for imaging and treatment of liver tumors.

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P 5

1H MRS SIGNALS FROM GLUTATHIONE MAY ACT AS PREDICTIVE MARKER OF APOPTOSIS IN IRRADIATED TUMOR

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Some tumor cells readily undergo apoptosis when exposed to ionizing radiation while others die by different pathways. It seems that inhibition of apoptosis in tumor cells depends at least in part on intracellular GSH level.
In the present work, the level of GSH were studied by means of 1H MRS in two cell lines, MCF-7 and HeLa from cervix cancer that show different radiosensitivity. Irradiation of cells resulted in a time dependent decrease of cell viability, much stronger in HeLa than in MCF-7.
Annexin test showed that the fraction of apoptotic cells after irradiation in HeLa cells is much higher than in control samples (33.2 ± 6.1 %, at 24 hr after irradiation). On the contrary, MCF -7 cells did not show a significant increase in apoptosis with respect to not-irradiated cells.
MRS signals from GSH (G) show much lower intensity in HeLa with respect to MCF-7 cells while the opposite is true for free glu (g). G/g ratio decreases after irradiation in MCF-7 cells while it slightly increases in irradiated HeLa cells. Treatment of MCF-7 cells with 100 M of BSO resulted in an increase of cell radiosensitivity and of the percentage value of annexin-V positive cells (36± 5.7 %). In parallel the ratio G/g in BSO treated MCF-7 behaves as in HeLa cells.
This study indicates that GSH depletion could be bound to a protective role against apoptosis, and its level may act as predictive marker of apoptosis by irradiation.

P 6

CALCULATION OF RBE'S FOR 125I AND 103PD BRACHYTHERAPY SOURCES IN THE APPLICATION OF PERMANENT PROSTATE IMPLANT

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Both 125I and 103Pd sources have been widely used in the permanent prostate implant. An important consideration for the choice of brachytherapy sources, as well as for the comparison of permanent implantation with external beam radiotherapy, is the relative biological effectiveness (RBE) for the source/seed used in the implantation. The prescription for the prostate implant is currently based on the dose distribution desired for the treatment. The dose at each point is contributed from the surrounding seeds. To evaluate the effective RBE from seeds, we have calculated the RBE's for both 125I and 103Pd at various radial distances to the seed surface. In this study we examined the microdosimetric properties of 125I and 103Pd. Monte Carlo simulation was performed for photons emitted from 125I and 103Pd seeds. Energy depositions from photons and all their secondary electrons were tracked. Dose distributions of lineal energy, d(y), were calculated for spheres of 1 um in diameter and at various radial distances to the seed surface. From the dose distribution of lineal energy, the dose mean lineal energy, yD, was derived. For sparsely ionizing radiation, RBE is proportional to the microdosimetric parameter, yD. Using 60Co as a reference radiation, the RBE's for 125I and 103Pd were then determined as a function of radial distances to the seed surface. The results showed that the RBE values are constant in the distance range from 0.5 to 5 cm. In this distance range, a RBE value of 2.2 is found for 125I, and 2.5 for 103Pd.

Q 1

ALPHA-PARTICLE RADIOBIOLOGICAL EXPERIMENTS USING THIN CR-39 DETECTORS

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In the present work, we prepared thin CR-39 detectors from commercially available CR-39 SSNTDs with a thickness of 100 um by etching them in 1 N NaOH/Ethanol at 40 °C to below 20 um. The desired final thickness was achieved within ~ 8 h. Such etching conditions can provide relatively small roughness of the detector as revealed by atomic force microscope, and thus provide transparent detectors for radiobiological experiments. As an example for practical use, custom-made petri dishes, with a hole drilled at the bottom and covered with a thin CR-39 detector, were used for cell culture. Photographs of the cells and alpha-particle tracks together were taken under the optical microscope, which allowed the hit positions on the cells by the alpha particles to be determined accurately. The integrity of DNA was studied for the risk assessment.

Q 2

RADIATION EFFECTS IN CULTURED TUMOR CELLS EXAMINED BY 1H MRS: MOBILE LIPIDS MODULATION AND PROLIFERATIVE ARREST

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Much attention has been devoted in the past to monitor changes of mobile lipid (ML) 1H MRS signals, mostly triglycerides (TG), present in spectra of tumor cells. High-intensity ML signals are typical of cells with a high percentage of S- and G2+M phases, while cells mostly in G1-phase had low ML signals. In the present study, we studied the 1H MR spectra of cultured HeLa and MCF-7 cells to relate variations of ML signals to metabolic changes produced by irradiation and accompanied by delays in cell cycle phases.
A G2 arrest is observed for both cell lines after irradiation. In HeLa cells, a considerable amount of DNA fragmentation in a sub G1 peak is also visible. This result points to the presence of apoptosis in HeLa cells as confirmed by Annexin V test.
Irradiated HeLa cells present less intense ML signals with respect to controls. The opposite is true for MCF-7 cells. Modulation of ML intensity with time was modelled by considering that the rate dL/dt of accumulation of reserve lipids (L), such as TG and consequently ML, is given by the difference of the rate of lipid production R1 and the rate of lipid consumption R2: dL/dt = R1 -R2. Both rates decrease linearly with time as a consequence of cell proliferation slowing down (G1 phase increase) in control samples. After irradiation, fitting parameters show different behavior in MCF-7 and in HeLa cells after irradiation that can be attributed to a different balance of lipid production and consumption.

Q 3

FLUORESCENCE AS A INDICATOR OF RADIO-INDUCED BIOLOGICAL DAMAGES

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The exposure of biological materials to ionising radiation leads to a loss of functionality, due to the modification of critical structures. In space applications, the complexity of the radiation environment requires special techniques to detect radiation damages to living organisms. The goal of this research is to develop a new technique to evaluate radio-induced damages on photosyntethic organisms. This new approach is based on the detection of fluorescence signal emitted by the multi-enzymatic complex, responsible of photosynthesis: the Photosystem II (PSII). Automatic devices able to monitor the physiological state at the level of PS II directly under radiation exposure, have been developed. According to this technique, fluorescence change, index of biological damage, is studied as a function of the absorbed dose. The effects of radiation on photosynthetic processes have been studied both on whole organisms and on the multi-enzymatic complex PSII, extracted from the photosynthetic cells.
In the first case, the purpose is to select the photosynthetic organisms that are most resistant to the radiation, in view of the production of oxygen and biomass during long space missions. In the second case, the damage on the extracted Photosystem II particles may give an indication of the absorbed dose.

R 1

RADIATION PROTECTION: DIFFUSE/DIRECT RADIATION QUANTIFICATION WITH OLD TECHNIQUES AND NOVEL PROCEDURES

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This work aims to present the development of measurement techniques of diffuse/direct radiation in the spaces where ionizing radiation are present.
It is common sense that, when dealing with radiation exposure, either in diagnosis or in therapy, it is imperative to quantify not only the radiation that is absorbed by the patient, but also the diffuse radiation that lasts in the space around him/her.
Diffuse radiation becomes really very important when it is meant to guarantee a correct and efficient screening on the areas that surround ionizing radiation sources, in order to meet safety standards for workers as well as the general public.
We present two different methods of radiation quantification: a direct method, that applies the transmission coefficient concept, by using an optical system for reading exposed radiological films, and an indirect method, that applies de Beer law, supported by an interpolation algorithm.
The direct method applies basic physical concepts and technologies, but in a different set up arrangement, that is now making way to a quality certification. The indirect method, the development of an algorithm that allows the quantification on an alternative way, making use of a different physical concept and performing a calculation, helps to verify and complement the results obtained with the previous method.
By applying both methods, and a direct dose measurement, we can determine the relation between the optical density of the film, and the measured radiation dose, thus being able to contribute to radiation safety, with an old technique and a novel procedure.

R 2

NANODOSIMETERS BASED ON GEL SCINTILLATORS

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The measurement of the absorbed dose in nanometer-size targets is essential for the development of radiobiological models at the cellular level. Several techniques have been proposed to measure quantities related to the energy deposition in the different sensitive structures of the cell. The high-pressure recombination ionization chambers [1] and the ultraminiature proportional counters [2] have both the inconvenience to be based on tissue-equivalent gas mixture simulations. On the other hand, the solid-state microdosimeters, such as the thermoluminiscent detectors or alanine, need from detection models [3] to study their response, and to compare the energy depositions to water.

The inherent difficulty of solving aqueous radioactive solutions in organic scintillators has contributed to the development of efficient emulsifiers, such as the ethoxylated alkylphenol, which allows the incorporation of large amounts of water to aromatic hydrocarbons. For the modern scintillator concktails it becomes possible to confine the radioactive substance in micelles of nanometer-size.

Most of the commercially available liquid-scintillation counters are equipped with one external gamma-source, which can be applied to measure the degree of chemical quenching generated in the scintillator by the addition of the radioactive substance. As it will be proved in this work, quenching is intimately related to the amount of water incorporated to the scintillator, and consequently to the energy deposited inside the micellar structure.

Gel scintillators have also promising applications as electron and alpha-particle nanodosimeters, because the radioactive substance can be confined in micellar structures, without observing undesirably transferences of the sample to the detector. The deposited energy can simply be derived from the analysis of the deformations of the pulse-height spectra caused by quenching [4-6].

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R 3

DEVELOPMENT OF PHYSICAL AND NUMERICAL TECHNIQUES OF ALANINE /EPR DOSIMETRY IN RADIOTHERAPY

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The use of Alanine / EPR dosimetry technique in radiotherapy has been increasing in last years due to the easy use and manipulation as well the greater accuracy of the method. Although some real applications, the method needs further developments in order to increase the reliability and decrease the analyses time consuming. In this work, a set of fifty alanine dosimeters have been used in radiotherapy context, simulating a three-dimensional treatment in a non-overlapping dosimeter configuration. A Co60 source has been used in doses ranges from 0.1 Gy to 5 Gy with a maximum field aperture of 10 cm2. A calibration curve has been obtained from a wide dose range (from 0.1 Gy to 10 Gy). The dose reconstruction from physical and numerical simulation of the EPR signal can now be used to better adjust the error in calibration curve and gives a final accuracy near 0.01 Gy. Also, a complete set of experimental test parameters have been used with a standard dosimeter in order to obtain the best analysis configuration. These results indicate that for a conventional treatment of some decimeters of Gy this method can be useful, with a correct signal validation. In order to increase the process reliability, a numerical test and fitting software has been developed, based on the physical method and equipment constrains, producing a fast data analysis. With these results, the general use of the alanine / EPR dosimetry in radiotherapy context is discussed.

R 4

SINGLE-ION DOSIMETRY BASED ON FLOATING GATE MEMORIES

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A Flash memory cell is a MOSFET where a polysilicon layer (Floating Gate, FG) is interposed between the substrate and the "control" gate (CG) [1]. By storing electrons or holes in the FG, one can change the threshold voltage VTH of the MOSFET, thus permanently store a bit of information. Excess charge in the FG provides an electric field across the tunnel oxide (which separates the FG from the substrate). Therefore, every time a high LET ion impacts on a FG, it leads to severe charge loss from a programmed FG, hence in VTH from hit FGs [2]. In figure, we are showing that for a device irradiated with iodine ions having E=264MeV and LET=64MeVcm2/mg, VTH exceeds 4V. The VTH of the single FG cannot be read in commercial devices, which allow the user to access only a digital ("0" or "1") datum, so specialized equipments (using company-reserved algorithms) are needed to obtain these data. VTH linearly depends on ion LET, and is the effect of rather complex phenomena, instead than the simple effect of generation-recombination-drift of charges [3]. From the number of FG cells experiencing VTH one can accurately derive not only the fluence of ions impacting on the device, but also their spatial distribution with a sub-micrometer accuracy (being in this range the distance between adjacent FGs in a state-of-the-art technology). We are using this approach for an experiment on the NASA SET-1 satellite [4]. Further, one can in principle derive the LET of impacting ion from the VTH value.

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R 5

A TISSUE EQUIVALENT PROPORTIONAL COUNTER FILLED WITH A MIXTURE OF TE GAS AND 3HE FOR NEUTRON MONITORING.

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Tissue equivalent proportional counters (TEPC) allow the measurement of the absorbed dose and the ambient dose equivalent in mixed fields. IRSN has been studying since 2002 the design and the response of a TEPC in terms of neutron ambient dose equivalent H*(10) for dosimetry purposes at workplaces in nuclear industry.
First, a counter with a cylindrical geometry had been filled with a tissue equivalent gas propane based at a low pressure in order to simulate a 1 micron tissue site. The ambient dose equivalent measured in monoenergetic neutron fields underestimated the reference more than 50% at low energies (< 500 keV). A small amount of 3He had been added to the tissue-equivalent gas (propane based) in order to increase the response at the lower energies of neutrons.
Measurements had been carried out in monoenergetic neutron fields and in a thermal neutron field. The underestimation observed at low energies decreased but the results were not totally complying with the objectives of neutron monitoring.
It was chosen to improve the analysis of the microdosimetric spectra y.d(y) (the dose mean lineal energy yD and the distribution of dose in y) in order to identify the energy of the incident neutrons. The determination of the energy range of the incident neutrons allows the weighting of the results and a best estimate of the ambient dose equivalent H*(10). This paper presents the different improvements and focuses on the last experimental results. These results are also compared to numerical data obtained from the Monte Carlo code MCNPX.

R 6

COINCIDENT CHARGE COLLECTION IMAGING OF A DE-E MONOLITHIC TELESCOPE WITH AN ION MICROPROBE

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In order to carry out risk assessment in radiation protection applications, it is necessary to develop instrumentation that is capable of measuring equivalent dose. As outline in NCRP report 137, the two prevalent methods of equivalent dose assessment are microdosimetry and the fluence approach. Each method requires unique instrumentation: micron sized sensitive volumes that measure ionisation energy deposition for microdosimetry, and particle telescopes that measure particle type and energy for the fluence based approach. Research into microdosimetry using silicon devices was pioneered by Dicello et.al and more recently Rosenfeld et.al. Agosteo et.al have recently taken a different approach, investigating the use of a DE stage of a monolithic DE-E detector as a microdosimeter in neutron fields. Such devices may also be used to obtain spectral information which can be used with the fluence approach. The aim of the current work is to investigate the charge collection behaviour of these monolithic silicon detectors using an ion microprobe; in particular we look at the charge sharing between DE and E stages and how this varies with ion type and location of ion strike on the device.

R 7

SIMULATION OF THE MEASURED IONIZATION-CLUSTER DISTRIBUTIONS OF ALPHA-PARTICLES IN NANOMETRIC VOLUMES OF PROPANE

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In the last years, the probability of the formation of ionization clusters by primary -particles at 5.4 MeV in nanometric volumes of propane (20.6 nm and 24.0 nm in a material of density 1.0 g/cm3) was studied experimentally and by Monte Carlo simulation, as a function of the distance of the centre line of the particle beam from the sensitive volume (SV). The Monte Carlo calculations were performed taking into account the single electron detection efficiency of the track-nanodosimetric counter, which was estimated on the base of Monte Carlo calculations of electron transport inside the detector. Due to the long drift distance (more than 20 cm), an exact treatment of the electron motion inside the counter was very time consuming and the approximation of disregarding the very weak radial component of the electric field was adopted in a wide region of the detector. With the availability of more calculation power, a new evaluation of the efficiency has been performed taking into account a more realistic description of the electric field inside the counter, pointing out a value lower than previously estimated. Besides, the efficiency of the counter in resolving temporally the collected electrons has been estimated, together with its effect on the measured distribution. On the base of these evaluations, a new comparison has been performed between measurements and calculations, pointing out a better agreement than previously estimated.

R 8

BAYESIAN RECONSTRUCTION OF NANODOSIMETRIC CLUSTER DISTRIBUTIONS AT 100% DETECTION EFFICIENCY

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Ionization measurements in nanometric simulated volumes at a given distance from a charged particle track make use of electron (or ion) gas detectors, having non-uniformly distributed detecting efficiency. Due to the inefficiency of the detector, the spectra obtained by such detectors should be properly processed in order to reconstruct the frequency distribution of clusters produced in the irradiated gas. Bayesian data analysis is particularly suited for this type of inverse problems. In a previous work we have applied a Bayesian unfolding to ionisation distributions due to 5.4 MeV a-particles in a 20 nm site obtained by Monte Carlo simulations, taking into account different detection efficiency conditions. We have demonstrated that, in the case of uniformly distributed efficiency, Bayesian analysis, with a proper choice of the prior distribution and of the number of points considered for the reconstruction, provides a valid tool for reconstructing the true ionisation distributions, well beyond the maximum measured cluster size. In the more realistic case of non-uniform detection efficiency a method, also based on Bayes' theorem, which makes use of a simplifying assumption about the possible repartition of the produced electron cluster in the sensitive volume (SV), provides a good estimation of the distributions due to a-particles passing outside the SV. In this work we will apply the same method to the distributions obtained by a-particles crossing the SV, taking into account the ionisation density profile of a particle track.

R 9

IONIZATION CLUSTER-SIZE FORMATION BY ELECTRONS: FROM MACROSCOPIC TO NANOMETRIC TARGET SIZES

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An indispensable prerequisite for a deeper understanding of specified physical, chemical or biological changes initiated in matter when exposing it to ionizing radiation is a detailed knowledge of particle track structure. Here, the structure of electron tracks is of particular interest since electrons are set in motion in large numbers as secondary particles during the slow down of any kind of ionizing radiation in matter. From the point of view of radiation induced early damage to genes and cells, which starts with the early damage to segments of the DNA molecule, the most effective secondary electrons are those at energies of a few hundred eV since the yield of double-strand breaks induced by such electrons in the DNA shows a maximum. This can be explained by the fact that in water cylinders, 2 nm in diameter and height (as a substitute to small segments of the DNA), the probability of the electron-induced formation of ionization cluster sizes greater than or equal to two is highest also at initial electron energies of a few hundred eV.
In view of this promising feature of ionization cluster-size distributions formed by low-energy electrons in nanometric targets of liquid water for explaining particular radio-biological endpoints, it is the aim of the present work to investigate the properties of cluster-size formation by electrons as a function of target size. Here, main emphasis is laid on the behaviour of cluster-size distributions if the target size is reduced from macroscopic to nanometric volumes.

R 10

DOSES AND LET SPECTRA IN THE BEAM OF 12C WITH ENERGY 500 MEV/AMU

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This contribution describes the results of experiment performed at the Joint Institute for Nuclear Research (JINR) in a 12C ion beam with primary nominal energy 500 MeV/amu. Dosimetric and microdosimetric characteristics are presented and analyzed. Absorbed depth-dose distribution was established by means of diamond detectors and the spectra of linear energy transfer (LET) were measured with the LET spectrometer based on chemically etched track detectors. Studies were performed from the beam entrance up to the region of the Bragg peak. The measured LET spectra were compared with theoretical calculations using program SRIM. A quite good agreement of both spectra is observed. The spectra vary with the depth - the average LET show increase with the depths, the spectra also broaden with the depth.

R 11

TWO MINIATURIZED TEPCS IN A SINGLE DETECTOR FOR BNCT MICRODOSIMETRY.

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Microdosimetry with Tissue Equivalent Proportional Counters (TEPC) has proven to be an ideal dosimetry technique for mixed radiation fields as those ones of BNCT. We have constructed a counter composed of two twin cylindrical mini TEPC inserted in a slim titanium sleeve of 2.7mm external diameter. This TWIN TEPC has been designed to perform dosimetry and microdosimetry in the Boron Neutron Therapy Capture (BNCT) intense radiation fields.
The two 0.6 mm3 mini-TEPC sensitive volumes centres are 1 cm apart. The two
cathodes are of A-150 tissue-equivalent plastic one of them is loaded with 50 ppm of 10B.
The TWIN-TEPC has been tested in gamma and neutron fields. The experimental data are presented and discussed. First measurements in TAPIRO reactor point out that the counter works properly at the maximum reactor power.

R 12

DEPENDENCE OF NANODOSIMETRIC SPECTRA ON THE SENSITIVE VOLUME LENGTH AND ION DRIFT IN AN ION-COUNTING NANODOSIMETER

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Nanodosimetry aims at evaluating radiation damage to the DNA, specifically, from measured cluster-size distribution of clustered ionizations (nanodosimetric spectrum) in a proper nanometer-scale sensitive volume (SV). Simulations performed for a gas-filled SV even showed a marked influence of its lateral extension on the initial particle direction. An ion-counting gaseous nanodosimeter (ND) permits establishing experimentally this dependence, which is important for carrying out precise measurements. In the ND, ions are detected after their drift in the gas; this permits selecting their origin (the SV) by the choice of the ion-counting time window. The realization of this possibility strongly depends on the velocity spread of the drifting ions. Detailed drift measurements of the propane-born ions in the ND were performed in comparison with argon-born ions, where the interpretation of the results is simpler. It was found, that, in spite of a large number of different ion species, the entire drift of propane-born ions in the ND, in a wide range of conditions, can be characterized by a single value of ion mobility, with a modest Gaussian-like broadening. This value (reduced to the same pressure) may be strongly different under different pressures and electric fields.
The possibilities and limitations of the SV selection based on the ion-drift timing will be analyzed and discussed. Monte Carlo simulations performed with measured drift velocity distributions will be compared with available experimental ND spectra.

R 13

THEORETICAL AND EXPERIMENTAL COMPARISON OF MOSFET MICRODOSIMETRY IN MICROBEAM RADIATION THERAPY (MRT)

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At the European synchrotron in Grenoble (ESRF), Microbeam Radiation Therapy (MRT) is being developed in in-vivo preclinical trials targeting brain tumors. MRT is being performed by using an array of microscopic-rectangular X-ray beams (typically 25-50 μm wide, 200 micron pitch, and 1 cm high), positioned close to each other, to irradiate a biological target. The microbeams are produced by a tungsten multi-slit collimator. The resulting dose distribution in the irradiated target is a comb-shaped superposition of the contributions from all microbeams. The Ratio of Peak-to-Valley Doses (PVDRs) in the composite distribution has been found to be of critical importance for the biological response of healthy and tumoral tissues to irradiation. The PVDRs are depending on microbeam width, X-ray energy used, and the separation between adjacent microbeams. MOSFET dosimeters can be used for relative dosimetry and thus determine PVDRs in a phantom typically made of PMMA. It has been found that the highest resolution is obtained when using the MOSFET chip in edge-on geometry so that the sensitive volume is parallel with the propagation of the beam. This work tried to find to what degree the directional dependence of the MOSFET perturbs the estimation of the PVDRs. A large number of PVDR measurements were performed when using two different kinds of multi-slit collimators.
Computationally, MRT dosimetry relies on Monte Carlo simulations. In the present work a Monte Carlo study was made of depth- and lateral-dose profiles for a single microbeam when scoring the dose in a simulated MOSFET-detector. Composite dose distributions from many microbeams were determined and PVDRs were calculated and compared with measured values.

R 14

OPTICAL IMAGES OF DOSE DISTRIBUTIONS IN GEL-FRICKE

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Aim of the study was i) the preparation of an optical pre-prototype scanner to perform 1D and 2D measurements of the radio-chromic Fricke-agarose-Xylenol Orange gel; ii) the examination of optical properties of the gel. In fact, the Fricke-agarose-Xylenol Orange gel has scarcely been examined with respect to its optical properties because in the past Fricke-agarose was examined mainly with respect to its properties for MRI scanning.
To obtain dose-response curves of the radio-chromic gel, we use a CCD based device designed for reading Gaf Chromic films, that we have modified to meet the optical properties of the dosimeter.
With a resolution of 0.18x0.18 mm2, the optimum range of doses in which p.u. is lower than 2% was 3-10 Gy. The minimum detectable dose estimated as the absorbed dose corresponding to 3 SD above background was 0.1 Gy . With a resolution of 1.98x1.98 mm2 the optimum range of doses in which p.u. is lower than 2% was 0.3-10 Gy. The minimum detectable dose estimated as the absorbed dose corresponding to 3 SD above background was 0.015.
The comparison with alanine dosimeters in the dose range 7-10 Gy showed agreement within a few percent and the same agreement was observed for the comparison with TLD in the range 1-3 Gy.

R 15

SENSITIVITY AND DYNAMIC RANGE OF FGMOS DOSIMETERS

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A new approach to dosimetry using an array of FGMOS memory cells [1-3] in the form of a commercial UVPROM (MC27C801 from ST Microelectronics) given special preparation is described. The 8 Mbit device is prepared as a dosimeter by dividing the memory cells into blocks with all the cells in each block programmed to store the same amount of charge on the floating gate, and the amount of charge stored in the cells in a given block is set to increase linearly with the block number. Reading the device as a memory yields a "0" for cells that still have more than a threshold amount of charge on the floating gate and "1" for cells whose charge has dropped below the threshold amount. Exposure to ionizing radiation causes cells to flip from the "0" to the "1" state, and as some blocks fill with cells in the "1" state others become partially filled maintaining a near constant rate of cell flipping with continued exposure. A plot of the number of "0" to "1" transitions induced by exposure to ionizing radiation is plotted versus the absorbed dose in the figure for three devices with slightly different preparations and readout. Methods for extending the sensitivity to lower doses and increasing the dynamic range will be discussed. These dosimeters provide a wide dynamic range with no fading due to annealing, non-destructive readout, a cross-sectional area of 1-2 mm2, and they require no power during exposure.

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R 16

AN IRRADIATION FACILITY WITH A HORIZONTAL BEAM FOR RADIOBIOLOGICAL STUDIES

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A facility with a horizontal beam for the radiobiological experiments was designed and constructed at the Heavy Ion Laboratory in Warsaw. The heavy ion beams from the U200-P Warsaw Cyclotrone are transported in a horizontal vacuum tube with conventional beam tuning components including a fast mechanical beam shutter which can be activated by the irradiation control system. After entrance collimation the beam is spread out passively by thin scattering foils (Au with thickness 50 - 20 mg/cm2) placed 2 m before the biological target. Multiscattering processes around 0o lead into good homogeneity of the radiation over an area of at least 1 cm2. A homogeneity of the radiation field better than ±3% has been achieved over the diameter of the irradiated biological targets of 50 mm using controlled x-y step motor. The on-line beam dosimetry is assured by two silicon detectors mounted at the 15o and 20o inside the scattering chamber. Simultaneously, the experimental output of the facility was proved by the appropriate Monte-Carlo multiscattering simulations. First irradiations of biological samples of the V79 cells have shown the functionality of the setup.

R 16

THE MICRODOSIMETRY OF LOW ENERGY PHOTONS IN RADIOTHERAPY

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Low energy photons are more and more used in radiotherapy, either in diagnostics in particular for mammography (10-28 keV) or in treatments using 125I (30 keV) or 103Pd (20keV) brachytherapy seeds. The RBE for these photons is not very well determined.
In this work, the photon spectra for the different sources have first been calculated using the EGSnrc MC code at different depths in tissue. These photon spectra are used as input for the event-by-event MC code TRION to calculate the microdosimetric lineal energy (y) distribution for each isotope. In parallel with the calculation of the microdosimetric spectra, our team has analysed the distribution of the size of the ionization clusters generated in structures between 1 and 10 nm of radius using TRION to generate particle tracks of the secondary electrons in water vapour .
The microdosimetric dose average lineal energy, yD, calculated in a sphere of 1 m is 3.5keV/ m for 125I, 4 for 103Pd and between 4.5 and 5 for mammography spectra. yD was found to diminish slightly with the distance from the seed for 103Pd, due to the hardening of the radiation. The same effect is observed in mammography with penetration depth. The mean cluster orders for 10 nm regions are 3.0 for Pd, 3.3 for I and around 3.1 for mammography. Calculated quality factors indicate a value of about 1.4 which should be adopted for mammography.

SINGLE CELL DOSIMETRY FOR RADIOIMMUNOTHERAPY OF B-CELL LYMPHOMA PATIENTS WITH A LEUKAEMIC SPREAD OF THEIR DISEASE

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Many lymphoma patients have both tumours and a leukaemic spread of their disease, that is, they have a significant amount of tumour cells circulating in the blood stream. To optimise radioimmunotherapy for these patients there is a need for cellular dosimetry. In this work the effects of different uptake patterns (internalising and non-internalising MAbs) and variation in cellular size were analysed for two low energy electron-emitters. The amount of cross absorbed-dose to tumour cells was also estimated.
Method: The energy deposition from electrons uniformly distributed in the cell and on its surface was Monte Carlo simulated. Cells were assumed to be spherical with radii of 6.35, 7.7 and 9.05 micrometer (radius of Raji cells: 7.7±1.35 micrometer). The simulated electrons were mono-energetic with energies of 18 keV and 28 keV, corresponding to the mean energy per decay for 125I and 123I, respectively. Absorbed fractions, absorbed doses and dose-volume-histograms were generated.
Results: The absorbed dose per decay for the 18 keV electrons varied between 0.369-1.407 mGy/Bq s, depending on cellular size and uptake pattern. Corresponding values for the 28 keV-electrons were 0.334-0.860 mGy/Bq s. The cross-absorbed dose is negligible compared to the self-absorbed dose.
Conclusion: The cell size influences the absorbed dose by up to a factor of 2.5, whereas the uptake pattern by 1.7. The largest absorbed dose per decay to a cell circulating in blood is received for an internalising MAb labelled to 125I and it is 60% higher than the 123I case which, however, gives a more uniform absorbed dose distribution.

MODELING LUNG CANCER INCIDENCE IN RATS FOLLOWING EXPOSURE TO RADON PROGENY

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Lung cancer incidence in Sprague-Dawley rats was simulated by a biologically-based carcinogenesis model, which is formulated mathematically in terms of a stochastic state-vector model (SVM). This model, which describes the random movement of cells through a series of initiation and promotion states, was validated by comparison with in vitro transformation data. In the present application to in vivo carcinogenesis, the response by an organized tissue was considered by the incorporation of stimulated mitosis through cellular inactivation, removal through lysis and subsequent differentiation.
While transition rates between the various states of the SVM are expressed as functions of dose, lung cancer incidences for radon progeny exposures are commonly expressed in terms of Working Level Months (WLM). Doses to sensitive target cells in the bronchial epithelial tissue of the rat lung were calculated by a stochastic dosimetry model, considering the distinct monopodial branching structure and the crossfire of alpha particles from alveolar tissue to bronchiolar airways. Doses to bronchial and alveolar cell nuclei could reasonably be approximated by lognormal distributions, with geometric standard deviations (GSD) between 7 and 10, depending on exposure conditions.
Based on a dose-exposure conversion factor of about 7 mGy/WLM and a GSD of 8, lung cancer incidences were calculated for each cumulative exposure category in the experimental study, consisting of different exposure rates and exposure times. Fair agreement could be observed between experimental data and theoretical predictions over the whole exposure range. For the smallest exposures and exposure rates, the model predicts the experimentally observed dose-rate effects.

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S 3

TRANSFORMATION IN TARGET CELLS WITH DIFFERENT GEOMETRIES DUE TO RADON PROGENY IN THE HUMAN LUNG

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To assess the risk due to inhaled radon progeny in the human lung, ICRP [1] focussed on the layers containing the target cells, i.e., the basal and secretory cells. Such an approach did not consider details of the sensitive cells in the layers. The present work uses the microdosimetric approach and determines the linear energy transfer (LET) in the target cells. Cell nuclei were "formed" randomly along the tube wall in the layer recommended by ICRP [1]. An effect specific track length model [2,3] was then used to determine the transformation frequencies. Basal cells are close to irregular cones while secretory cells are close to ellipsoids so there is a reason to assume that the cell nuclei are not spherical. The purpose of this study is to investigate the effects of the geometry of basal and secretory cells on the transformation frequencies.

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S 4

CFD AS A TOOL IN RISK ASSESSMENT OF INHALED RADON PROGENIES

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Last decade, Computational Fluid Dynamics (CFD) technique proved to be a powerful tool in the modelling of biological processes and design of biomedical devices. In this work, a CFD method was applied to model the transport of inhaled air and radioactive particles within the human respiratory tract. A finite volume approach of FLUENT CFD code was used to compute the flow field characteristics in the lumen of the first five airway generations of the tracheobronchial tree, leading to the right upper lobe. Large numbers of inhaled particles were tracked to model the transport and deposition of radon progenies on the bronchial walls. The size distribution and activity concentration of radon daughters, characteristic to uranium mines and homes were taken from the published literature. Primary deposition patterns and activity distributions were computed. Highly inhomogeneous deposition and activity patterns were found with hot spots in the vicinity of the carina ridges. The outcomes of present modeling efforts can serve as input data in lung cancer risk analysis. The integration of the present CFD model with the hit probability computing and state vector model of carcinogenesis leads to a biophysical mechanisms-based complex risk model of radon inhalation.

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Addendum to ***"Book of Abstracts"***
POSTER PRESENTATIONS

(Missing in the "Book of Abstracts" due to a typesetting error)

A 8

HEAVY ION TRACK STRUCTURE SIMULATIONS IN LIQUID WATER AT RELATIVISTIC ENERGIES

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A 25

ELECTRON TRACK SIMULATION USING ETMICRO

Eun-Hee Kim
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B 3

THEORETICAL MODELING OF RADIOLYTIC DAMAGE OF FREE DNA BASES AND WITHIN DNA MACROMOLECULE.

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B 4

SIGNIFICANCE OF 8-OXOG IN THE SPECTRUM OF DNA DAMAGES CAUSED BY IONIZING RADIATION OF DIFFERENT QUALITY.

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R 17

CELLULAR MICRODOSIMETRIC EVALUATION OF THE INFLUENCE OF IRRADIATION SPECIFICITY IN ALPHA RADIOIMMUNOTHERAPY

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R 18

IMPROVED MEASUREMENTS OF NEUTRON DOSE EQUIVALENT RATES USING A DUAL INSTRUMENT TECHNIQUE

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A 8

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Track structure simulations are a useful tool in Radiation Biology to provide information on spatial distributions of energy deposition patterns and on the production of radiation damage to DNA and other cellular structures. These computer codes use Monte Carlo methods and follow the primary as well as secondary particles event-by-event, from starting energies to total stopping. Relativistic heavy ions (or HZE particles) are of special interest to NASA and their vision of human deep-space travel like the mission to Mars. HZE particles are part of deep-space Galactic Cosmic Rays which are deflected by Earth's magnetic field. Therefore little is known on their interaction with the human body.
Interaction cross sections for bare (i.e. fully ionized) heavy ions are obtained within the plane-wave Born approximation from proton interaction cross sections by scaling laws. We have modified and updated our model of the dielectric response function of liquid water to reflect the new available data from inelastic X-ray scattering (IXS) experiments using synchrotron radiation. Proton interaction cross sections have been recalculated using this new model for the dielectric response function together with a fully relativistic plane-wave Born approximation which includes medium polarization effects like the Fermi-density effect in a consistent way. The new cross sections have been implemented into the track structure simulation code PARTRAC. PARTRAC is now able to simulate relativistic protons and bare heavy ions from several 100 keV/nucleon up to several GeV/nucleon.

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A 25

ELECTRON TRACK SIMULATION USING ETMICRO

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A new Monte Carlo code ETMICRO (Electron Transport code for MICROdosimetry) is now available for tracing the electrons down to 10 eV in liquid water. ETMICRO employs much the same frame of track construction as the previous programs by considering total 11 (5 ionization, 5 excitation and 1 elastic) scattering modes. It is updated in a sense that the most recent suggestion on the Drude model parameters by Emfietzoglou (*Radiat Res 163, 98-111, 2005*) has been adopted in generating the inverse mean free path (IMFP) data and the corresponding differential values (DIMFPs). The elastic scattering cross sections originate from various literatures. ETMICRO has been compared with MOCA8B and PITS in terms of X_{90} values for 100- to 10000-eV primary electrons. ETMICRO and PITS show similar patterns in X_{90} values varying with the primary electron energy but three-times differences in absolute values. The potential of electrons causing direct damage on DNA has been estimated as functions of the electron energy and the distance of DNA from electron in an arbitrary direction, which are in turn utilized to assess the DNA damage by an electron cloud of a spectral energy. ETMICRO is to be extended to cover the physicochemical process of electron interactions with water molecules and to totalize the indirect and direct damages on DNA.

B 3

THEORETICAL MODELING OF RADIOLYTIC DAMAGE OF FREE DNA BASES AND WITHIN DNA MACROMOLECULE.

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The yield of base damages in living cell caused by ionizing radiation is about several orders of magnitude higher then yields of single and double breaks of DNA strands. Experimental yields of modified bases determined in free bases and in the double stranded DNA show striking differences in yields of particular stable products of radical attack. The attempt to explain these differences is made with help of theoretical calculations.

The yields of reactions of the most important radiolytic product, OH· radical, with individual nucleobases, nucleosides and short DNA oligomers are predicted using stochastic model. The diffusion of radicals produced by water radiolysis is simulated by Monte Carlo technique, radical reactions with particular atoms of bases and deoxyribose is calculated according to Smoluchowski theory. The relation between spatial limitations for radical approach to particular reaction sites within DNA and the yields of damaged bases is resolved. The reaction probabilities with particular sites within nucleobases, nucleosides and DNA oligonucleotides are compared to available experimental yields of base damages.

B 4

SIGNIFICANCE OF 8-OXOG IN THE SPECTRUM OF DNA DAMAGES CAUSED BY IONIZING RADIATION OF DIFFERENT QUALITY.

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The yields and composition of DNA damages caused by ionizing radiation depend on radiation quality. With increasing LET, the proportion of isolated DNA damages decreases with respect to clustered damaged sites. Poor efficiency of repair of complex lesions increases the probability that lesions persist through DNA replication, lead to the generation of mutations and thus contribute to deleterious biological effects of ionizing radiations (e.g. Weinfeld *et al.* 2001, Rad. Res. 156, 584).
The most important product of oxidative damage to DNA bases is 8-oxo-7,8-dihydroguanine (8-oxoG). The excision of 8-oxoG is retarded if an abasic site or strand break is present close on opposite strand (Pearson *et al.* 2004, Nucleic Acids Res. 32(1), 263). The modeling of DNA damage induced by ionizing radiation of different quality was performed to assess frequencies and composition of complex damages containing 8-oxoG. Track structures of chosen charged particles with LET in the range 0,4-160 keV/μm were obtained using the Monte-Carlo code TRIOL (Bigildeev and Michalik 1996, Rad. Phys. Chem. 47(2), 197). The molecular structures of studied DNA oligomers with different base sequences were built up by molecular modeling software Amber 7.
Distributions of single strand breaks on opposite DNA strand around induced 8-oxoG have similar shape for different ionizing radiation, but differ by their occurrence in the whole spectrum of DNA damages. The most probable configuration is a strand break localized in position ±3 bases from 8-oxoG. The calculated data will be presented and analyzed with respect to available experimental information about their repair capacities.

R 17

CELLULAR MICRODOSIMETRIC EVALUATION OF THE INFLUENCE OF IRRADIATION SPECIFICITY IN ALPHA RADIOIMMUNOTHERAPY

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The purpose of this study was to evaluate the dosimetric consequences of alpha-immunotherapy improvements. We focused on the influence of irradiation specificity on the absorbed dose at the cellular scale.
We considered:
- different configurations (single cell, monolayer or cluster of cells),
- different radionuclides,
- different cellular sizes,
- different affinities and numbers of binding sites for the labelled antibodies.

We carried out our calculations with a microdosimetric model using the Monte-Carlo software MCNPX (version 2.5.e). We considered two kinds of treatment: one with non-specific and one with specific labelled antibodies. We calculated the specific energy spectra in the cell nuclei and evaluated an enhancement ratio (ER), i.e the ratio of absorbed dose in the specific situation on the absorbed dose in the non-specific situation.
Considering a single cell of cellular radius of 10µm and nuclear radius of 5µm wich presents a number of binding sites of 2.10^5 and a solution of antibodies labelled with bismuth 213 (concentration: 0,1 nM) with an affinity constant of 5.10^8 liters/mol, ER > 2,1. For the same cell and antibody in a compact monolayer, ER >14. Finally, an ER of 25 was calculated for cells located in the core of a 100 µm radius cluster with a packing factor of 0.5 and considering an homogeneous diffusion of antibodies.
This study highlights the impact of geometry modelling on dosimetric results at the cell level for alpha-immunotherapy.

R 18

IMPROVED MEASUREMENTS OF NEUTRON DOSE EQUIVALENT RATES USING A DUAL INSTRUMENT TECHNIQUE

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The health risk posed by the irradiation of human tissue by neutrons is highly complex. This is amply illustrated by the neutron fluence to ambient dose equivalent (H*(10)) conversion coefficient and its variation with neutron energy. This coefficient varies by a factor of two over the seven decades of neutron energy between 10^{-9} and 10^{-2} MeV, but then increases by a factor of forty between 10^{-2} and 1 MeV. Between 1 and 10 MeV, however, the coefficient only varies by 10%.

It is little wonder, therefore, that traditional neutron area survey meters (comprising a detector sensitive to thermal neutrons surrounded by moderating material) have responses that deviate significantly from the above form. These instruments perform well in fields dominated by neutrons in the 0.5 to 5 MeV range, but at intermediate energies they may over-respond to such a degree that their response in a (relatively soft) workplace neutron field could be high by a factor of two or more.

Tissue-equivalent proportional counters (TEPCs) also have problems with their ambient dose equivalent response. The TEPC simulates energy deposition in microscopic tissue volumes by using a low-pressure TE gas inside a TE counter wall. This works well at higher neutron energies (0.5 MeV and above), but seriously under-responds at intermediate energies (by factors of 10 or more).

This presentation describes a technique that utilises the different responses of the above instruments to provide more accurate measurements of H*(10) in workplace neutron fields. Limitations and suggestions for further work will also be discussed.

CORRIGENDA
to
"Book of Abstracts"
POSTER PRESENTATIONS

F4

THE SENSITIVITY OF THE ALKALINE COMET ASSAY IN DETECTING DNA LESIONS INDUCED BY X RAYS, GAMMA RAYS AND ALPHA PARTICLES

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Single cell gel electrophoresis, also known as comet assay, has been shown to be a sensitive method for the analysis of induction and repair of DNA strand breaks and oxidative DNA lesions. The alkaline comet assay was applied here to detect DNA breaks induced by different types of radiation. The goal was to demonstrate if different energy deposition patterns of photon radiation with varying energies (29 kV, 220 kV X rays; Co-60 -, Cs-137-γ-rays) and alpha-radiation from an Am-241 source and from Bi-213 bound to antibodies against the cellular adhesion molecule E-cadherin result in DNA lesions, which can be quantified by the comet assay either by the radiation specific dose effect relationship or their repair kinetics. Radiation experiments were performed with human lymphocytes exposed to X and gamma rays (0.5 Gy – 3.0 Gy) and with a human gastric cancer cell line (HSC45-M2) exposed to alpha particles (Am-241: 0.5 – 3.0 Gy; Bi-213: activities from 1.6 MBq – 9.9 MBq). Cs-137-γ-rays were used as a reference radiation. DNA damage was quantified by three parameters: %DNA in the tail, tail length and tail moment according to Olive. Data were fitted and compared using a multiple linear regression model. The comet assay data for %DNA in the tail and tail moment did not indicate any difference in the initial radiation damage produced by 29 kV X rays relative to the reference radiation types, 220 kV X rays and the gamma rays, either for the total dose range or in the low-dose range. In contrast, when fits of tail length data were performed, saturation appears for X rays but not for gammas. The exponential term, which models the bending over the dose response in the fit, is significantly different from zero for the X rays but not for the gamma rays. This result may be interpreted to indicate that X rays induce smaller DNA fragments or more strand breaks at low doses. Best-fit calculations for the repair kinetics do show a tendency that for irradiation with 29 kV X rays, repair of damaged DNA proceeded slightly more slowly in the first 10 to 20 minutes but this result was not statistically significant. Data for both alpha exposures showed a significant increase in DNA damage only at high doses (>2 Gy Am–241; >1.6 MBq Bi-213), but the damage at 2 Gy exceeded the damage induced at 2 Gy by Cs-137-γ-rays by a factor of 2.5. Experiments involving other DNA damage indicators such as chromosomal aberrations detect a significant increase in DNA damage at much lower doses, i.e. at 0.02 Gy Am-241 or 18.5 kBq of Bi-213. These results indicate that differences in biological effects must arise through downstream processing of complex DNA damage, which is not detected by the alkaline comet assay.

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