AIR² Access to INFRASTRUCTURES for Radiation protection Research

Issue 4
February 2016

Editorial

Today, I have great pleasure in announcing the birth of AIR²D². This is not a new ersatz of a Star Wars creature but our brand new "Access to Infrastructures for Radiation protection Research Documented Database" http://www.concert-infrastructures.eu/.This dissemination tool aims to be simple and user-friendly, providing each user with easy access to the description and localisation of large sets of infrastructures. It combines searchable tables and maps, including descriptions of each infrastructure according to recommended criteria. Search results can be exported (CSV/excel files).

This is a living database that will be enriched by all the improvements and contributions that you make, allowing new and well-described infrastructures to be added daily.

Dr Laure Sabatier - CEA

The floor to...

In autumn 2015, all efforts within CONCERT WP3 were directed to the preparation of research topics for the first CONCERT call. In August 2015, the radiation protection research platforms MELODI, EURADOS, NERIS and ALLIANCE prepared research priority statements, listing high priority topics in radiation protection research, each in their own research area. With the help of associations active in the field of medical applications of ionising radiation, the focus was further expanded. Integration of research in social sciences and humanities is taken on board as well.

" Further harmonisation of quality standards, practices and protocols in relation to the use of infrastructure, data acquisition and data storage is an invaluable prerequisite to further solve the puzzle in radiation protection research."

In parallel with the above-mentioned efforts, the CONCERT Management Board (MB) also proposed research priority topics of European interest to WP3.

More than fifty research priority topics were collected! However, careful analysis revealed a high degree of overlap between the research priorities proposed by the platforms and the MB. And many topics were considered to profit from merging. Elimination of topics that might be funded through other sources further reduced the number.

Finally, the MB agreed that the number of call topics should be very limited to avoid fragmentation of funding. The MB also encouraged formulation of interdisciplinary research topics, to stimulate integration.

Brainstorming in WP3 revealed two research call topics, unanimously accepted by the MB. WP3 then submitted the call topics to WP4, to administer the call. The floor is open for excellent multidisciplinary research consortia to fill the knowledge gaps in radiation protection!

What about infrastructure in future research projects? Further harmonisation of quality standards, practices and protocols in relation to the use of infrastructure, data acquisition and data storage is an invaluable prerequisite to further solve the puzzle in radiation protection research. Taking into account relevant information from existing databases and biobanks, and careful selection of infrastructures and protocols, will help the integration between future results and existing data.

Access to unique large infrastructures is sometimes quite a challenge. Via its WP6 dedicated to facilitate access to infrastructures, CONCERT will be the optimal medium to coordinate and negotiate access in such cases.

Dr Nathalie Impens - SCK•CEN
CONCERT WP3 Leader
« Priority research and Joint programming needs in the perspective of European Integration »

Photo: © SCK•CEN

CONCERT CORNER

Future events:

15 Feb 2016: ExB Meeting, Pavia, Italy

16 Feb 2016: MB Meeting, Pavia, Italy

WP 6 News:

16 Feb 2015: WP6 Work session:
15:30-18:30, Pavia, Italy

AIR²D²: Access to Infrastructures for Radiation protection Research Documented Database is now opened and available on : www.concert-infrastructures.eu

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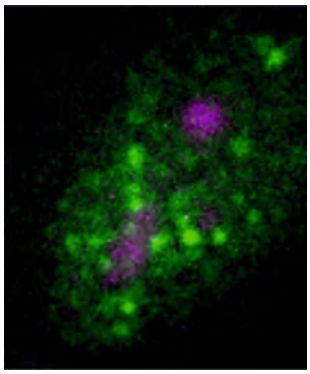
This project has received funding from the Euratom research and training programme 2014-2018 under grant agreement No 662287

SNAKE

Munich Ion Microbeam Irradiation Facility

The ion microprobe SNAKE (Superconducting Nanoprobe for Applied nuclear (German: Kern) physics Experiments) is installed at the 14 MV Tandem Accelerator in Garching near Munich and can be used for material analysis as well as for radiation biology research. The sub-micrometer beam size allows the targeted irradiation of single defined cells but also of more complex samples with single or counted ions, making it a suitable tool for low and high dose research. SNAKE provides protons and heavier ions with a wide energy range and thus LET range (2-2000 keV/µm), as follows:



Photo, C. Siebenwirth/UnibwM

Targeted irradiation (green cross) of a nucleolus (purple) in a cell nucleus

- protons: 4 – 28 MeV
- d, He, B, C, O: 2 – 10 MeV/nucl
- heavier ions: 0.2 – 4 MeV/nucl

By scanning the ion microbeam to irradiate one spot after another with a predefined pattern without targeting, it is possible to irradiate several cm² of cell cultures, tissues and small animals. The maximum ion range is obtained with protons, allowing irradiation of samples of up to 5 mm thick, such as 3D tissues, mouse ears or tumours. The heavier ions are more suitable for the exposure of single cell layers due to their lower range.

The live cell imaging setup with temperature control was designed for the irradiation of living cells with online monitoring. It can be used for targeted irradiation of single cells or even cellular substructures like mitochondria or nucleoli with a targeting accuracy <2 µm. Furthermore, it enables kinetic and dynamic studies of cell reactions, such as the (sequential) recruitment of several repair factors after DNA double-strand break induction.

Photo: UnibwM

Guenther Dollinger

At SNAKE, LET dependent studies using low and high LET particles can be used for intercomparison studies, in particular to investigate various endpoints of cell reactions after irradiation, especially at low doses.

Using the chopper-buncher system installed at the tandem accelerator, it is possible to form a short pulsed proton beam of about 1 ns duration at the target station of SNAKE. Using the focusing system of SNAKE, up to 20 Gy can be delivered in a single proton pulse to a beam spot of about 100 µm. This can be used to investigate ultra-high dose rate effects when irradiating from low to high doses.

The Facility offers access to the SNAKE microbeam, including all possible irradiation modes as described above, to potential users. Especially low-dose effects, also in the framework of bystander research, can be studied. In addition, for radiobiological experiments at SNAKE, access is provided to the biolab, including the cell cultures that have been developed, cell containers and irradiation and/or biological protocols. The user support staff are experienced in developing new irradiation as well as biological protocols as required, and in implementing and performing these protocols in collaboration with the external users.

SNAKE irradiation facility

Photo: T. Naeser/MAP

ID Card:

Exposure type:
External

Source:
14 MV Tandem Accelerator

Dose rate:
Single ion irradiation up to 10^9 Gy/s

Irradiation type:
Ions (protons, Li, C, …)
LET: 2-2000 keV/µm
Range < 5mm
Horizontal beam
Microbeam < 1 µm
Targeting accuracy < 2 µm

Irradiated organism type:
Cells, tissue, small animals

Address:
Maier-Leibnitz-Laboratorium (MLL),
85748 Garching, Germany

Access:
Joint research collaborations only, 3-6 beam times/yr

Supporting lab:
Cell culture

Internet link:
https://www.unibw.de/lrt2/forschung/snake

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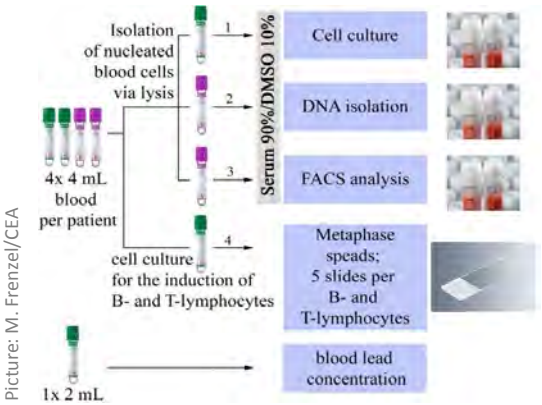
Related to:
MELODI, EURADOS, ALLIANCE

MICROIRRADIATION OF CELLS WITH ENERGETIC HEAVY IONS. Hauptner et al. 2004, Radiat Environ Biophys 42:237-245
LIVE CELL IMAGING AT THE MUNICH ION MICROBEAM SNAKE – A STATUS REPORT. Drexler et al. 2015, Radiat Oncol. 18;10:42

French Haemangioma Cohort and Biobank

Cohort for low-dose study long-term after radiation therapy

The risk of exposure to low doses of ionising radiation below 100 mSv is still controversial and highly discussed since especially its effect on the appearance of long-term pathologies might be larger than assumed. There is evidence that exposure to low doses increases for example the cancer risk but this effect is less pronounced and concurs with other confounding factors such as smoking. Actually, most model calculations are based on in vitro experiments.



Picture: M. Frenzel/CEA

Scheme of the FHC blood biobank

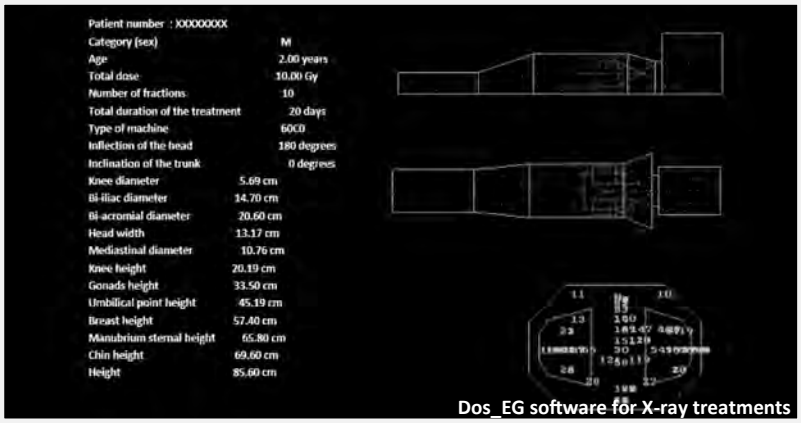
In France, children presenting with a skin haemangioma during early childhood were treated with radiotherapy from 1940-1973. Epidemiological analyses of this cohort have demonstrated a 3-fold higher risk of developing cancer (especially skin, breast and thyroid cancer). The French haemangioma cohort (FHC) is exceptional as it fulfils all necessary characteristics for low dose studies. It allows joint epidemiological and biological analyses to be performed for direct radiation risk assessment and the study of radiation-induced pathologies, due to accurate dosimetry calculations (i.e. the dose received at all major organs, taking into account the size of the baby/child during treatment) thanks to access to radiotherapy medical records. The FHC is very homogeneous, representing a normal healthy population characterised only by a haemangioma. It contains not only patients who received radiotherapy from different sources (^{226}Ra, X-rays, ^{32}P, ^{90}Y or ^{90}Sr) but also untreated individuals or those who received cryotherapy and serve as internal controls. A long-term post-irradiation follow-up exists.

A biobank for the FHC blood samples was set up through collaborations between INSERM (U1018, Florent de Vathaire) and the CEA (Radiation and Oncology Laboratory, Laure Sabatier) during the EU project, EpiRadBio. Only donors who received radiotherapy before the age of 3 years were selected, together with respective non-exposed controls. This biobank contains cytogenetic slides of metaphase spreads for T- and B-lymphocytes as well as isolated nucleated blood cells frozen in liquid nitrogen under conditions (10% DMSO in serum) to allow future cell culture experiments and DNA and FACS analyses to be undertaken. Supplementary information on confounding factors is available for every donor thanks to a questionnaire. This includes body weight and size, type of work, smoking and consumption of alcohol, (for women) number of pregnancies, appearance of cancer/benign tumour, radiological procedures during lifetime, chronic diseases, phototype and skin type. Additionally, the blood lead concentration at the time of blood donation has been determined. All this information is essential to distinguish the effect of radiation treatment from that of other factors which might influence cancer development.

Photo: Hartmuth Schröder

Monika Frenzel

The FHC allows in vivo studies and the identification of biomarkers to develop efficient models for long-term risk estimation for pathologies induced by low doses of ionising radiation, even a long time after exposure.



Dos_EG software for X-ray treatments

Picture: F. De Vathaire/INSERM

ID Card:

Cohort type:
French haemangioma cohort (humans, French citizens), 8335 subjects (5744 treated with radiotherapy), Brachytherapy (^{226}Ra, ^{32}P, ^{90}Y, ^{90}Sr) and X-ray (local treatment for skin haemangioma)

Age:
- at exposure: Starting from early childhood, mostly treated before the age of 15 years (7800 subjects, of whom 5473 received radiotherapy)
- currently: 42-75 years old

Biobank available:
Yes, 369 subjects (231 women, 138 men) of whom 70 non-exposed and 299 exposed subjects (under the age of 3 years; 261 donors <100 mSv, 38 donors 100 mSv; mean bone marrow dose)

Sample type:
Frozen nucleated blood cells (for cell culture, DNA/FACS analysis), cytogenetic slides with metaphase spreads of T- and B-lymphocytes

Sample storage conditions:
-20°C, liquid nitrogen

Conditions of use:
External use possible (via a selection committee)

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Related to:
MELODI, EURADOS, CARPEM

RADIOTHERAPY AS A RISK FACTOR FOR MALIGNANT MELANOMA FOLLOWING CHILDHOOD SKIN HEMANGIOMA. Haddy N et al. Melanoma Res. 2012, 1, 77-85.
ASSESSING CANCER RISKS OF LOW-DOSE RADIATION. Mullenders L. et al. Nature Reviews Cancer. 2009, 9, 596-604.

Dose Estimate, CABAS and NETA

Statistical and software tools for cytogenetic biodosimetry

Cytogenetic methods of biological dosimetry are crucial for triage of individuals following suspected radiation overexposure and also to support large scale research projects where biological markers of exposure and effect are required (see issue 1 – RENEB). The biological and statistical methods for dose estimation in radiation cytogenetics are now extremely well defined. To facilitate dosimetry, calibration data are collected and fitted under

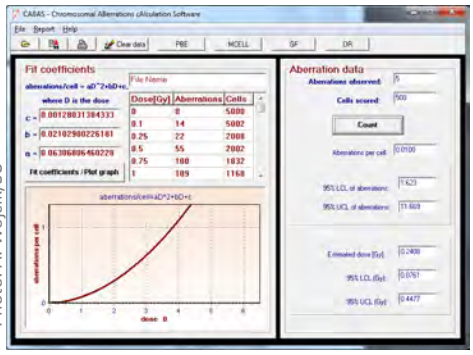

Photo: A. Wojcik/SU

The interface of CABAS

Poisson assumptions to a linear or linear quadratic model and the coefficients are then used to calculate doses. Full details of this classical procedure can be found in the International Atomic Energy Agency manual (http://www-pub.iaea.org/MTCD/publications/PDF/EPR-Biodosimetry%202011_web.pdf).

Statistical methods for analysis of cytogenetic data can be complex – for instance iteratively reweighted or maximum likelihood methods to fit calibration curves - however good statistical analysis is crucial to ensure that accurate dose and uncertainty estimates are produced. Thus in recent years there has been a lot of work on developing computational tools to support implementation of the IAEA statistical analysis methods. In particular, Dose Estimate and CABAS allow users to fit calibration curves and estimate whole or partial body doses in acute or protracted scenarios. Both tools contain graphic user interfaces for ease of use, come with full instructions, and have been extensively tested. Dose Estimate can be obtained by emailing liz.ainsbury@phe.gov.uk and CABAS from http://www.ujk.edu.pl/ibiol/cabas/. In addition, there are a large number of inhouse tools developed at the various biodosimetry laboratories in Europe, for instance GLIM (UAB), MLREG (BfS), BIODOSEUAB and DOSGEN (CPHR).

Photo: left to right:K. Rothkamm/ Hamburg University; A.Wojcik/SU

Liz Ainsbury - Andrzej Wojcik

Limitations in the traditional methods, for instance departure from Poisson distribution in partial body exposures, have led to development of new analysis methods based on alternative models to Poisson. NETA allows users to test whether data are Poisson or Neyman A distributed, for example: http://www.ujk.edu.pl/ibiol/neta/. Bayesian analysis is a very attractive solution to characterise cytogenetic doses, as the results are given in terms of probability distributions which intrinsically include uncertainty information. CytoBayesJ (liz.ainsbury@phe.gov.uk) and the R software radir (https://cran.r-project.org/web/packages/radir/index.html) are simple tools for this purpose.

Software tools have also been developed to assist in triage categorisation – including the Multibiodose EU FP7 project software (http://www.multibiodose.eu/software.html) and outside the EU, BAT and FRAT (https://www.usuhs.edu/afrri/biodosimetrytools).

Finally, in addition to defined tools, the retrospective dosimetry community has a number of biostatisticians devoted to analysing data and developing statistical analysis methods and tools. These experts are very happy to collaborate going forward – contact the authors or through RENEB (reneb@bfs.de).

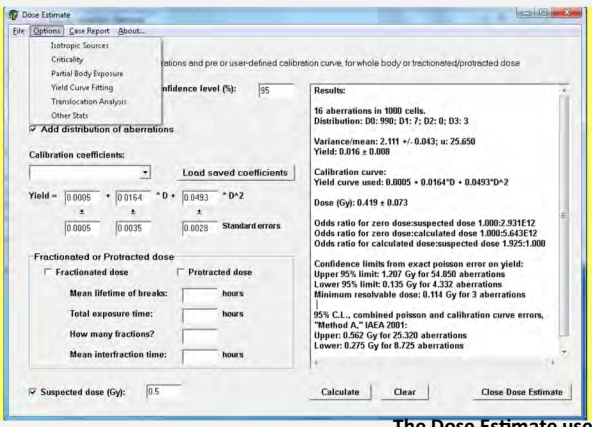

Photo: L.Ainsbury/PHE

The Dose Estimate user interface

ID Card:

Purpose:
Cytogenetic radiation dose and uncertainty assessment

Capacity:
N/A - freeware

Use:
Graphic user interface providing simple tools to fit calibration curves and estimate cytogenetic radiation doses

Housed by:
Dose Estimate: PHE;
CABAS: SU and JKU

Training proposed on the software:
Full instructions and example data are provided, but adhoc training can be given if needed

Access:
Dose estimate: Free, by emailing liz.ainsbury@phe.gov.uk;
CABAS: Free to download from: http://www.ujk.edu.pl/ibiol/cabas/ or by emailing andrzej.wojcik@su.se

Contact:
Dose Estimate: liz.ainsbury@phe.gov.uk, 0044 1235 825105;
CABAS: Andrzej.wojcik@su.se, 00468161217

Related to:
MELODI, EURADOS, CARPEM,

CABAS - A FREELY AVAILABLE PC PROGRAM FOR FITTING CALIBRATION CURVES IN CHROMOSOME ABERRATION DOSIMETRY. Deperas, J., et al. Radiat. Prot. Dosim. 2007 124:115-23.

DOSE ESTIMATION SOFTWARE FOR RADIATION BIODOSIMETRY. Ainsbury EA, Lloyd DC. Health Phys. 2010 98(2):290-5.

AIR²

Access to INFRASTRUCTURES for Radiation protection Research

Issue	Exposure platforms	Databases, Sample banks, Cohorts	Analytical platforms, Models, Tools
Published to date:			
Oct 2015, #1	FIGARO	FREDERICA	RENEB
Nov 2015, #2	B3, Animal Contamination Facility	The Wismut Cohort and Biobank	The Hungarian Genomics Research Network
Dec 2015, #3	Cosmic Silence	STORE	Metabohub
Feb 2016, #4	SNAKE	French Haemangioma Cohort and Biobank	Dose Estimate, CABAS, NETA
Coming soon:			
Mar2016, #5	GSI - Radon exposure facility	3 Generations exposure study	PROFI

Future events:

8-11 February 2016: Eurados Annual Meeting, AM2016, Milan, Italy

17-18 March 2016: 18th International Conference on Medical Physics, Radiation Protection and Radiobiology, ICMPRPR 2016, London, UK
Registration open until 17 Nov 2015 (paper submission)

24-25 March 2016: 18th International Conference on Radioactivity and Radiation Protection, ICRRP 2016, Madrid, Spain
Registration open until 24 Nov 2015 (paper submission)

April 2016: Deadline for the 1st Transnational Call for Proposals of EJP CONCERT

10-15 April 2016: 1st International Conference on Radioanalytical and Nuclear Chemistry, RANC-2016, Budapest, Hungary
Registration: open

9-13 May 2016: 14th Congress of the International Radiation Protection Association, IRPA14, Cape Town, South Africa
Registration open until 1st May 2016

4-8 Sept 2016: 42nd Annual Meeting of the European Radiation Research Society, ERR2016, Amsterdam, Netherlands
Registration open

19-23 Sept 2016: Radiation Protection Week, RPW2016, Oxford, UK.

3-5 Oct 2016: International Conference on Research Infrastructures, ICRI2016, Cape Town, South Africa.

5-7 Dec 20156: 8th EAN_{NORM}, Stockholm, Sweden.
Call for papers open

Editorial Committee: Jean-Michel Dolo, Elisabeth May, Laure Piqueret-Stephan, Laure Sabatier

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