DE LA RECHERCHE À L'INDUSTRIE

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Radiobiology

Space

Radiation protection

Laure SABATIER

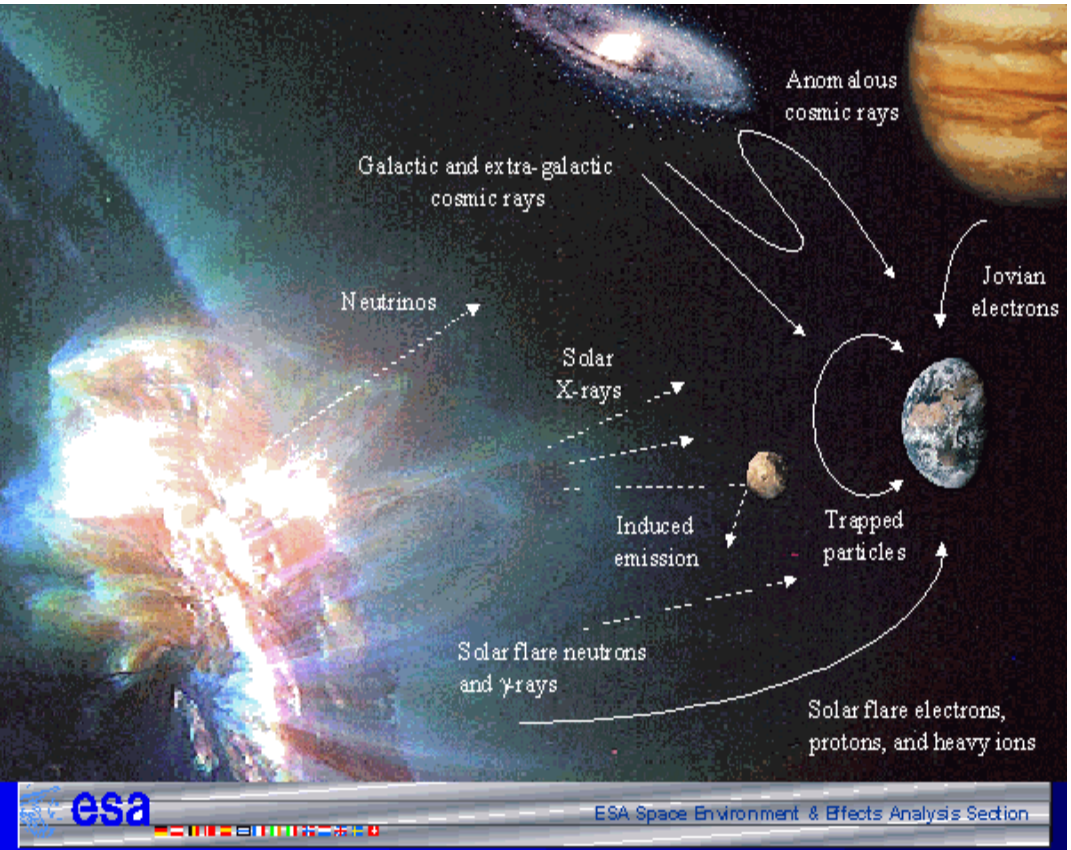
Chania
August 29, 2017

IONS OF HIGH-LET IN SPACE

- Particles trapped in Earth magnetic fields : Van Allen belts (electrons, protons = H 600 MeV, few ions)
- Solar radiation : neutrons, γ, protons, α particles and ions (E -> 1 GeV)
- Cosmic and galactic rays :

2% electrons and positrons

98% particles : - 87% protons
- 12% alphas
- 1% heavier ions



Ions are ~1% of the radiations but can represent up to 50% of the total dose

↳Increased risk of biological damage for long-term flights (Mars > 1% cells hit)

SPACE RADIOBIOLOGY : HOT TOPIC

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Healthy offspring from freeze-dried mouse spermatozoa held on the International Space Station for 9 months

Sayaka Wakayama[a,1], Yuko Kamada[b], Kaori Yamanaka[c], Takashi Kohda[d], Hiromi Suzuki[e], Toru Shimazu[e], Motoki N. Tada[f], Ikuko Osada[f], Aiko Nagamatsu[g], Satoshi Kamimura[b], Hiroaki Nagatomo[a,h], Eiji Mizutani[b], Fumitoshi Ishino[d], Sachiko Yano[g], and Teruhiko Wakayama[a,b,1]

If humans ever start to live permanently in space, assisted reproductive technology using preserved spermatozoa will be important for producing offspring; however, radiation on the International Space Station (ISS) is more than 100 times stronger than that on Earth, and irradiation causes DNA damage in cells and gametes. Here we examined the effect of space radiation on freeze-dried mouse spermatozoa held on the ISS for 9 mo at –95 °C, with launch and recovery at room temperature. DNA damage to the spermatozoa and male pronuclei was slightly increased, but the fertilization and birth rates were similar to those of controls. Next-generation sequencing showed only minor genomic differences between offspring derived from space-preserved spermatozoa and controls, and all offspring grew to adulthood and had normal fertility. Thus, we demonstrate that although space radiation can damage sperm DNA, it does not affect the production of viable offspring after at least 9 mo of storage on the ISS.

Space radiobiology needs realistic hypotheses and relevant methodology

Mélanie L. Ferlazzo[a] and Nicolas Foray[a,1]

"If humans ever start to live permanently in space" and to verify whether assisted reproductive technology is safe in space, Wakayama et al. (1) maintained freeze-dried mouse spermatozoa in the International Space Station for 9 mo. While these authors are aware of the risks linked to space radiation, both their rationale and methodology approach raise two concerns.

First, protracted exposure to radiation is known to cause radiation-induced cancers and cataracts, at least, and represents one of the major risks for space crews. This is notably a severe limit for a mission to Mars (2). On Earth, the natural radiation background (NRB) varies from 0.5 mSv/y (Japan) to more than 70 mSv/y (e.g., Ramsar, Iran) (3). By omitting the solar particle events (SPE), and by considering the dosimetry data of all missions of the spatial history, the average exposure to radiation in space is ≈ 0.4 mSv/d, 146 mSv/y (4). Consequently, a 9-mo space mission corresponds to an exposure of 109.5 mSv but also to 1.5 y spent in Ramsar. Hence, when the authors report that the low dose rate in space is 100 times higher than on Earth, they omit the highest NRB where there is no evidence of significant hazard (3). By contrast, the authors admit that a cumulated dose higher than 400 mGy may be hazardous (1). Such a dose corresponds to a 2.7-y space mission and 5.7 y spent in Ramsar. Why did the authors not expose their DNA samples to the highest-NRB areas to verify the measurability of their data before exposing them to space? How do we extrapolate the risks for a 2.7-y mission that may be hazardous from the nonsignificant data obtained for a 9-mo mission?

Second, the authors also examined the impact of space radiation upon fertility. However, there is no evidence that the highest NRB leads to mutations that propagate to the offspring. Furthermore, literature shows that only doses greater than 350 mGy cause reversible human aspermia, and aspermia may be permanent after more than 2,000 mGy (5). An exposure to 109.5 mSv is very far from these doses. Hence, to evaluate the impact of space radiation upon fertility a much longer mission would have been more relevant. Again, equivalent experiments performed in the highest-NRB areas can be useful, notably to better evaluate the impact of SPE.

We are fully aware that biological experiments in space are very difficult to set up. However, while there will always be a fascination of the general public for space, scientists should take particular care to justify their methodology and moderate their conclusions with regard to space radiobiology.

Acknowledgments

This work was supported by the Commissariat Général à l'Investissement through the INDIRA project and by the Centre Nationale d'Etudes Spatiales.

1 Wakayama S, et al. (2017) Healthy offspring from freeze-dried mouse spermatozoa held on the International Space Station for 9 months. *Proc Natl Acad Sci USA* 114:5988–5993.
2 Cucinotta FA (2015) Review of NASA approach to space radiation risk assessments for Mars exploration. *Health Phys* 108:131–142.
3 UNSCEAR (2011) Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. Annex D: Sources and effects of ionizing radiation (United Nations Scientific Committee on the Effects of Atomic Radiation, New York).
4 Maalouf M, Durante M, Foray N (2011) Biological effects of space radiation on human cells: History, advances and outcomes. *J Radiat Res (Tokyo)* 52:126–146.
5 Ash P (1980) The influence of radiation on fertility in man. *Br J Radiol* 53:271–278.

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Author contributions: M.L.F. and N.F. designed research, performed research, analyzed data, and wrote the paper.
The authors declare no conflict of interest.
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REPLY TO FERLAZZO AND FORAY:

About the Space Pup project

Sayaka Wakayama[a,1], Yuko Kamada[b], Kaori Yamanaka[c], Takashi Kohda[d], Hiromi Suzuki[e], Toru Shimazu[e], Motoki N. Tada[f], Ikuko Osada[f], Aiko Nagamatsu[g], Satoshi Kamimura[b], Hiroaki Nagatomo[a,h], Eiji Mizutani[b], Fumitoshi Ishino[d], Sachiko Yano[g], and Teruhiko Wakayama[a,b,1]

We would like to thank Ferlazzo and Foray (1) for their very important comments and suggestions. We will keep in mind that "scientists should take particular care to justify their methodology and moderate their conclusions."

One concern of Ferlazzo and Foray (1) is that our control experiment entailed exposure to the ground radiation of Japan, rather than to a high natural radiation background (NRB), such as Ramsar.

As the authors suggest, it would have been a good idea to expose our control sample to both Ramsar and Japan. When the control radiation level increases from 0.5 mSv/y (Japan) to 70 mSv/y (Ramsar) the difference between space and ground radiation will largely decrease. As mentioned in our paper, we concluded that regarding the use of a higher difference in radiation between space and a low-NRB location (Japan) "it does not affect the production of viable offspring after at least 9 mo of storage on the ISS [International Space Station]." (2) Thus, even if we use a high-NRB location as a control our conclusion will probably not change.

Ferlazzo and Foray (1) also point out the following: "Hence, when the authors report that the low dose rate in space is 100 times higher than on Earth, they omit the highest NRB where there is no evidence of significant hazard." We regret not knowing the location. However, to find small effects derived from space radiation it might be better to make a comparison between a low-NRB location and space.

The authors were also concerned about how one can "extrapolate the risks for a 2.7-y mission that may be hazardous from the nonsignificant data obtained for a 9-mo mission." We regret not being able to explain it very well in our paper. We had planned to conduct our Space Pup project for a longer period. However, our mission is still ongoing, as shown on a NASA web page (https://www.nasa.gov/mission_pages/station/research/experiments/893.html), and our sample will be returned to Earth after a longer exposure to space radiation.

Due to the restrictions placed on using the ISS we must demonstrate that our project is going well without any problems. For this reason, we need to publish our first data immediately to justify keeping the other space sample on the ISS for a longer period.

Another concern is the fertility of space-preserved sperm. The authors suggested that "aspermia may be permanent after more than 2,000 mGy" and that "exposure to 109.5 mSv is very far from these doses."

We thank them for this suggestion. The effects of radiation on live animals and frozen cells are known to be different (3). Freeze-dried sperm cannot repair DNA damage during space flight; therefore, the damage will be greater than that in live animals. Nevertheless, our data (178 mSv) are inadequate to predict the actual effects of space radiation. Therefore, the authors' following concern is perfectly valid: "Hence, to evaluate the impact of space radiation upon fertility, a much longer mission would have been more relevant." As mentioned above, we are already conducting a longer preservation experiment and will publish our conclusion upon completing the experiment.

1 Ferlazzo ML, Foray N (2017) Space radiobiology needs realistic hypotheses and relevant methodology. *Proc Natl Acad Sci USA* 114:E6733.
2 Wakayama S, et al. (2017) Healthy offspring from freeze-dried mouse spermatozoa held on the International Space Station for 9 months. *Proc Natl Acad Sci USA* 114:5988–5993.
3 Ohnishi T, et al. (2009) Detection of space radiation-induced double strand breaks as a track in cell nucleus. *Biochem Biophys Res Commun* 390:485–488.

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STUDY OF BIOLOGICAL EFFECTS OF HEAVY IONS FOR SPACE RADIOPROTECTION

- For most of biological effects studied, the Relative Biological Efficiency (RBE) of ions is > 1 (2 à 6), ↗ with the fluence and the LET, max between 100-300 keV/µm then ↘

- High-LET ions highly contribute to radiation space exposure: evaluate and understand the effects induced at various levels:

Single traversal
Low dose at tissue level

Physical and physico-chemical: initial effects
Molecular and cellular responses
Tissular response

- Identifying specific lesions (≠ from photons) and the molecular mechanisms involved in their genesis and repair

- Evaluate the long term response of cells/tissues exposed to ions: link to the carcinogenic risks following exposure to high-LET particles

ESA ROADMAP FOR SPACE RADIATION RESEARCH

Biological Effects

A1: Radiation response under spaceflight conditions
- Understand how cellular radiation response is affected by spaceflight environment
- Identify targets for therapeutic intervention

A2: Radiosensitivity & underlying mechanisms
- Characterize the sensitivity of medically relevant cells, tissues and whole organisms to cosmic radiation
- Determine the Relative Biological Effectiveness (RBE) factors of heavy ions for late effects, cancer and non cancer
- Quantify the effects of exposure to mixed high and low LET radiation field
- Elucidate the underlying molecular and cellular mechanisms

A3: Radiation Risk Assessment
- Determine the particle-dose dependency for acute effects
- Determine the effectiveness of GCR at low doses for carcinogenesis
- Determine the risk of CNS damage, non-cancer late effects from low doses of GCR

A4: Countermeasures
- Develop mitigation measures for radiation effects, including biomedical countermeasures
- Define the radiation dose limit for human space exploration

Radiation Physics

B1: Radiation environment
- Fully understand the radiation environment in space by determination of radiation field parameters

B2: Personal dosimetry
- Develop dosimetry capability to provide real time capability, which can be used in exploration missions

B3: Transport codes
- Fully model the radiation environments having respective transport codes benchmarked against physical/biological data

B4: Forecast
- Develop tools to forecast radiation environment of space missions and vehicles, for use in mission planning / operations

B5: Shielding
- Develop appropriate shielding materials and benchmark them with respective radiation codes

ESA PRIORITIES

- To provide quantitative estimates of the dose- and dose-rate dependence of the risk for radiation-induced acute and late morbidity, including cancer and noncancer effects

- To identify, develop and validate early biomarkers of risk for ensuing radiation-induced health detriment

- To identify, develop and validate biomedical and physical countermeasures, including the potential impact of individual susceptibility.

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BIOMARKERS

PERNOT ET AL, MUT RES 2012

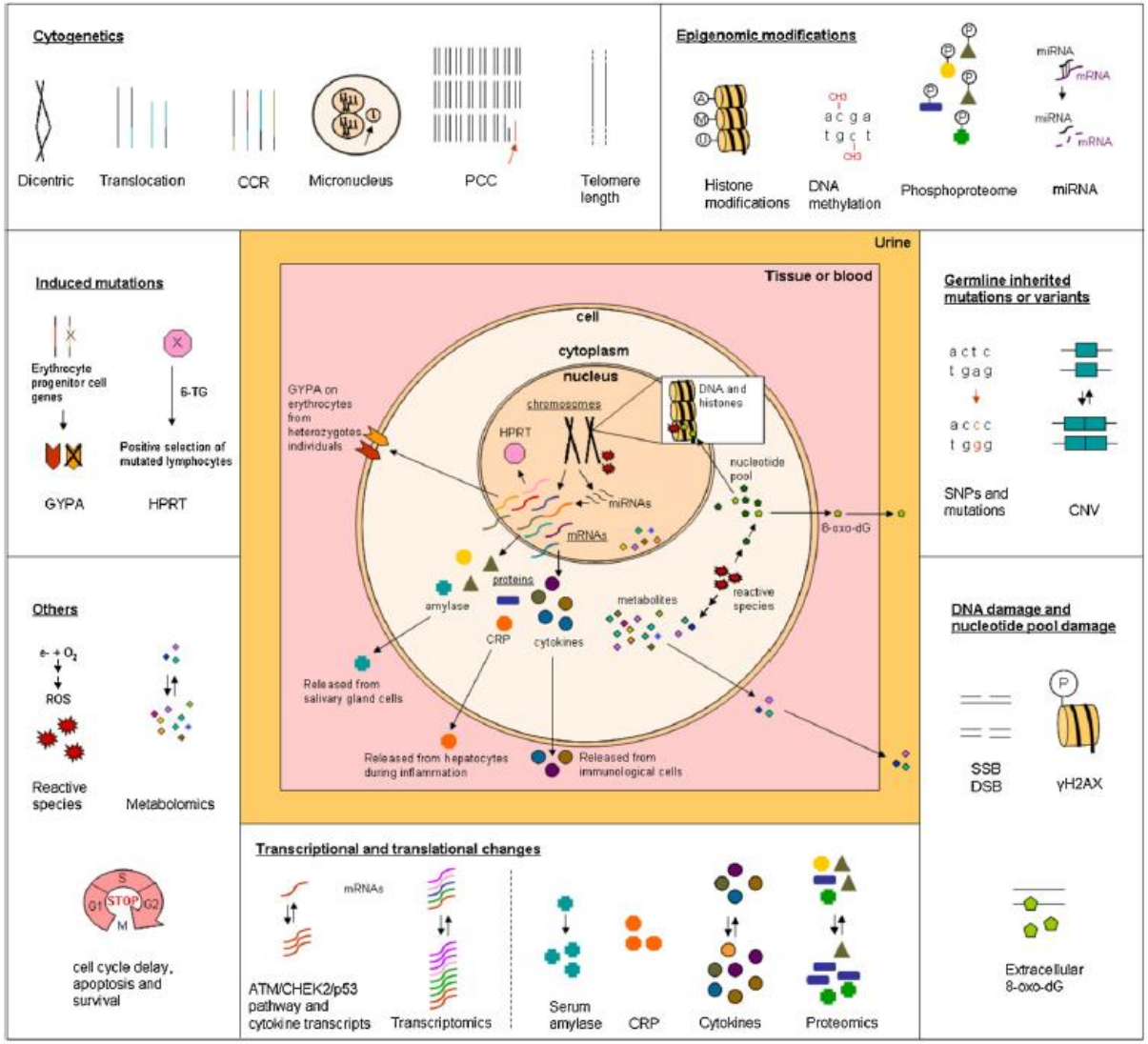


Fig. 5. Overview of the biomarkers of ionizing radiation covered in this review.
Vertical double lines represent pairs of chromosomes and horizontal double lines represent double strands of DNA.
A: acetyl group; CCR: complex chromosomal rearrangement; CNV: copy number variant; CRP: C-reactive protein; DSB: double strand break; GYPA: glycophorin A; HPRT: hypoxanthine-guanine phosphoribosyltransferase; M: methyl group; miRNA: microRNA; P: phosphate group; PCC: premature chromosome condensation; ROS: reactive oxygen species; SNP: single nucleotide polymorphism; SSB: single strand break; U: ubiquitin; 6-TG: 6-Thioguanine; 8-oxo-DG: 8-Oxo-deoxyguanosine.

Table 5
Temporal classification of IR biomarkers.

Biological classification of IR biomarkers		Temporal classification of IR biomarkers			
		Exposure	Susceptibility	Late effects	Persistent effects
Cytogenetics	Dicentrics	√	P	P[a]	P
	Translocations	√	P	P[a]	√
	CCR	√ (high LET IR)	P	P[a]	√
	PCC rings and fragments	√			
	Telomere length	P	P	P[a]	P
	Micronuclei	√	P	P[a]	
Nucleotide pool damage and DNA damage	SSB/DSB	√	P		
	γ-H2AX	√	P	P	P
	Extracellular 8-oxo-dG	(oxidative stress)	P		
Germline inherited mutations/variants and induced mutations	SNP, CNV and inherited gene mutations		√	P (minisatellites in offspring)	P
	CNA	P			P
	GYPA	√			√
	HPRT	√			√
Transcriptional and translational changes	Changes in the mRNA levels of the ATM/CHK2/p53 pathway	√	P		
	Changes in RNAs identified by transcriptomics	√	P	P	P
	Serum amylase	√			
	CRP	√			√
	Proteins identified by proteomics	P	P	P	P
	Cytokines	P	P	P	P
Epigenomic modifications	Histone modifications	P	P	P	P
	DNA methylation	P	P	P	P
	miRNA	√	P	P	P
	Phosphoproteomics	P	P		
Other biomarkers	ROS	√	P	P	P
	Metabolites and metabolomic	√	P	P	P
	Cell cycle delay, apoptosis and survival	P	P		
Direct dosimetry on samples	EPR/ESR	√			√
	Internal emitters	√			

√: direct evidence that this biomarker could be used as such; P: potential or theoretical use; CCR: complex chromosomal rearrangement; CNA: copy number alteration; CNV: copy number variant; CRP: c-reactive protein; DSB: double strand break; EPR/ESR: electron paramagnetic resonance/electron spin resonance; GYPA: glycophorin A; *HPRT*: hypoxanthine-guanine-phosphoribosyl transferase; IR: ionizing radiation; miRNA: microRNA; PCC: premature chromosome condensation; SNP: single nucleotide polymorphism; SSB: single strand break; ROS: reactive oxygen species.

[a] Chromosomal aberrations due to genomic instability.

BIOMARKERS

HALL ET AL, MUT RES 2017

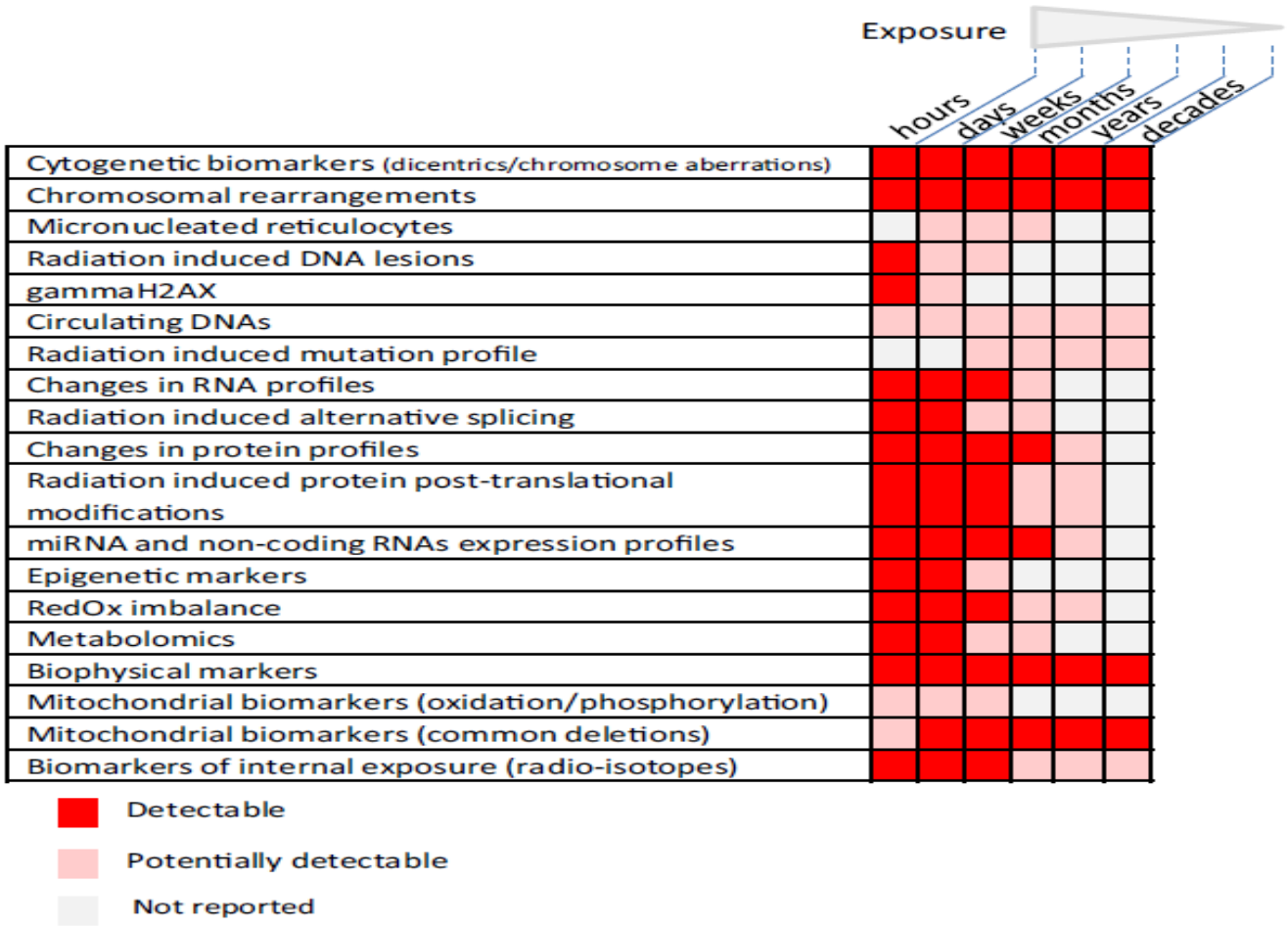


Fig. 3. Biomarker detectability with time.
This heatmap representation allows the selection of an appropriate biomarker with respect to time after exposure. Biomarkers were classified as easily detectable or potentially detectable with modern technology and assuming the availability of appropriate biological samples. It has to be noted that the majority of these biomarkers have yet to be validated using the proposed roadmap as a biomarker of low dose radiation exposure in human studies.

Table 1
Summary table of cytogenetic biomarkers.

	Exposure Assessment		Lower dose limit	Specific for Radiation quality	Partial Body exposure	Individual radio-sensitivity	Age dependent radiosensitivity in low dose range	Labor intensive	Automation possible	Applicable for large scale studies
	Past	Current								
Dicentrics	No	Yes	50 mGy[a]	Yes	Yes	No[b]	Yes	Yes if not automated	Yes (described for Giemsa stained dicentrics or by using PC and TC fluorescent probes)	Yes
Translocations	Yes (at group level)	Yes	300 mGy	Yes	Yes	No**	No	Yes	No	Yes
Intra-chromosomal aberrations	Yes	Yes	150 mGy	Yes	No	No	No	Yes	No	Yes
Micronuclei	Yes (only group level)	Yes	Several tens of mSv	No	No	No	No	No	Yes	Yes
MN-RET	Possibly (chronic genetic instability)	Yes Time dependent	10 mGy	Works after external and/or internal exposure	Bone marrow has to be exposed	Not tested	Not tested	No	Yes	Yes
Telomere length	No	No	Not assessed	No	Not assessed	Possibly	Probably No	Not assessed	Yes	Yes

[a] Requires the evaluation of 10,000 cells to evaluate exposures to 50 mGy.
[b] Radiation sensitive syndromes such as ATM and NBS homozygote carriers do show increased levels.

HIGHLY DAMAGED CELLS in COSMONAUTS LYMPHOCYTES

		flight	cells scored	cells with aberrations	dicentrics	centric rings	excess acentrics rings, minutes	range of breaks per abnormal cell
F1	after	2 weeks	657	1	0	1	0	2
F2	after	3 weeks	1000	5	2	1	2	1->2
R1	after	6 months	930	12	4	3	8	1->4
R2*	after	6 months	1020	11	5	2	4	1->2
R3*	before		1001	14	5	2	7	1->2
	after	6 months	1000	25	20	5	11	1->10
R4	after	6 months	982	7	3	1	3	1->2
R5*	after	6 months	685	11	9	3	17	1->20

Few cells are damaged,
Some have a very high level of damages

1

in 1

R1, R2, R4 30-40 mGy
R5 : 90 mGy
R3 200-300 mGy

Testard et al, IJRB, 1996

ONBOARD TISSUE-EQUIVALENT DETECTORS

Absorbed dose : 0,5 mGy/day

➔ equivalent dose : 1 mSv/day

Fluence : 2,4 . 10^4 particles/cm^2/day

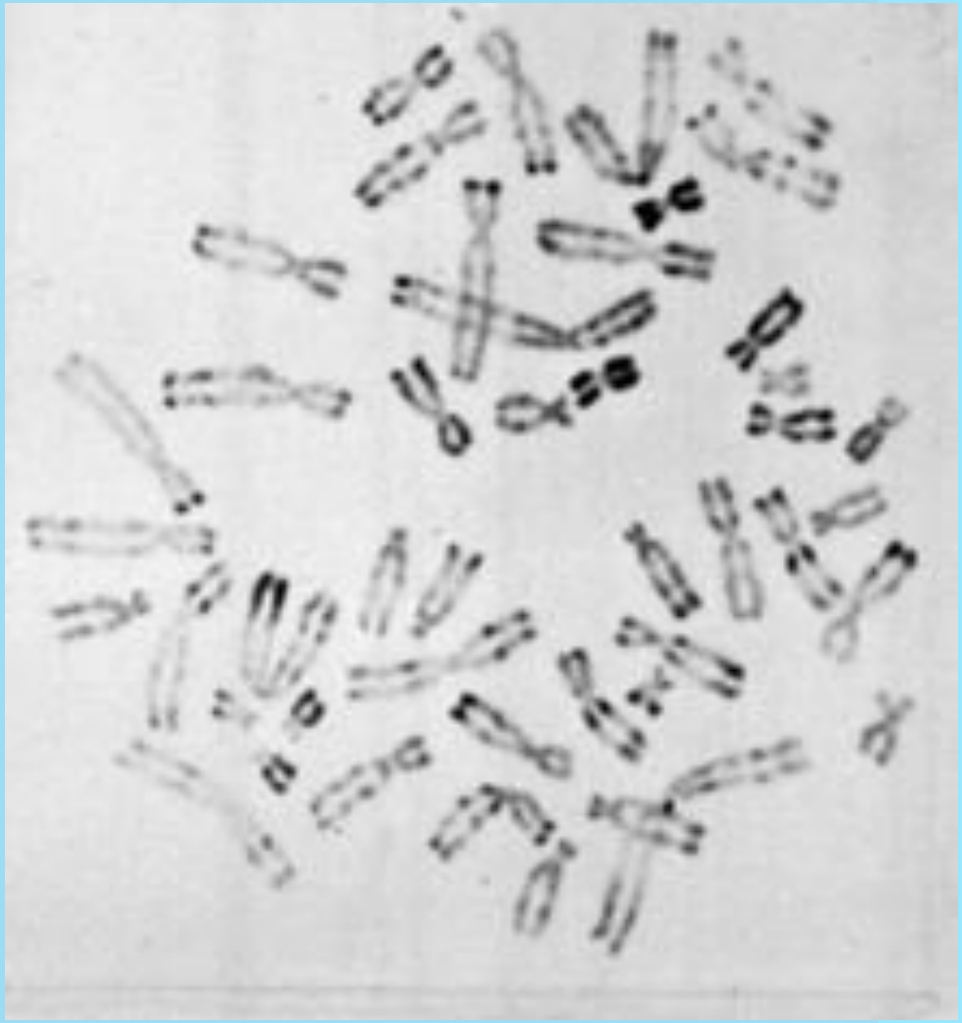
➔ for 6 months : 1 particle/nucleus (25 μm^2)

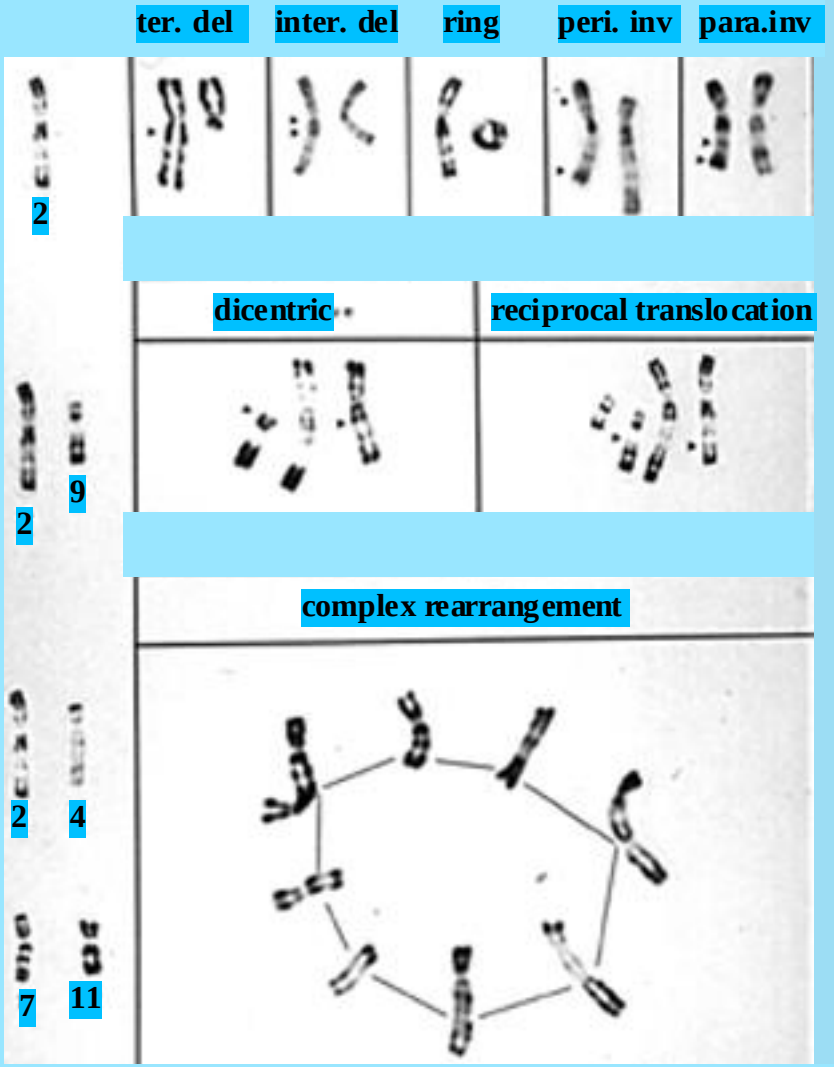
Mainly protons, for 6 months:

ions > 10 keV/µm	12 per 1000 cells
ions > 50 keV/µm	0.5 per 1000 cells

↳Increased risk of biological damage for long-term flights (Mars > 1% cells hit)

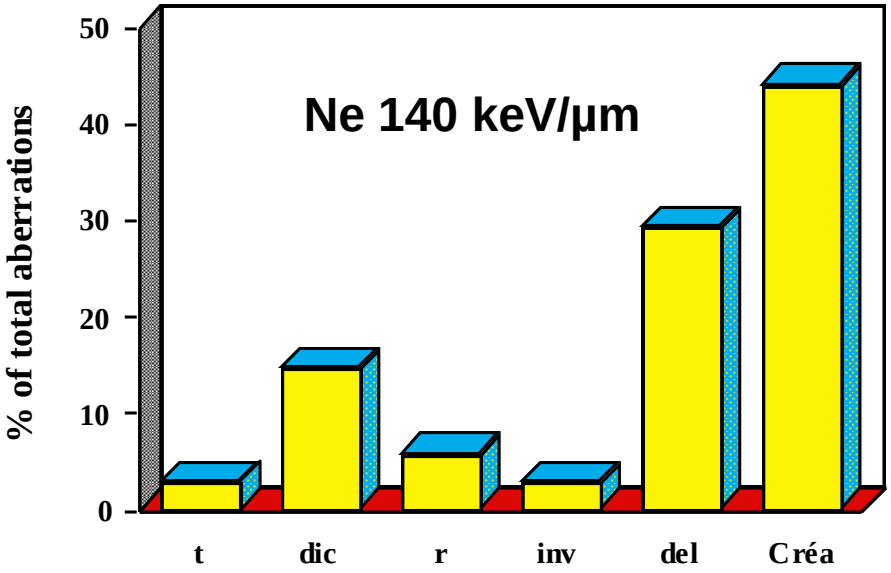
COMPLEX CHROMOSOME ABERRATIONS





Sabatier et al, 1987, Mut Res
Sabatier et al, Nature. 1992;357:548.
Martins et al, Mutat Res. 1993;285(2):229-37.
Martins et al, Mut Res 1994
Sabatier et al, IJRB. 1994. 66(5):611-3
Testard et al, IJRB, 1997

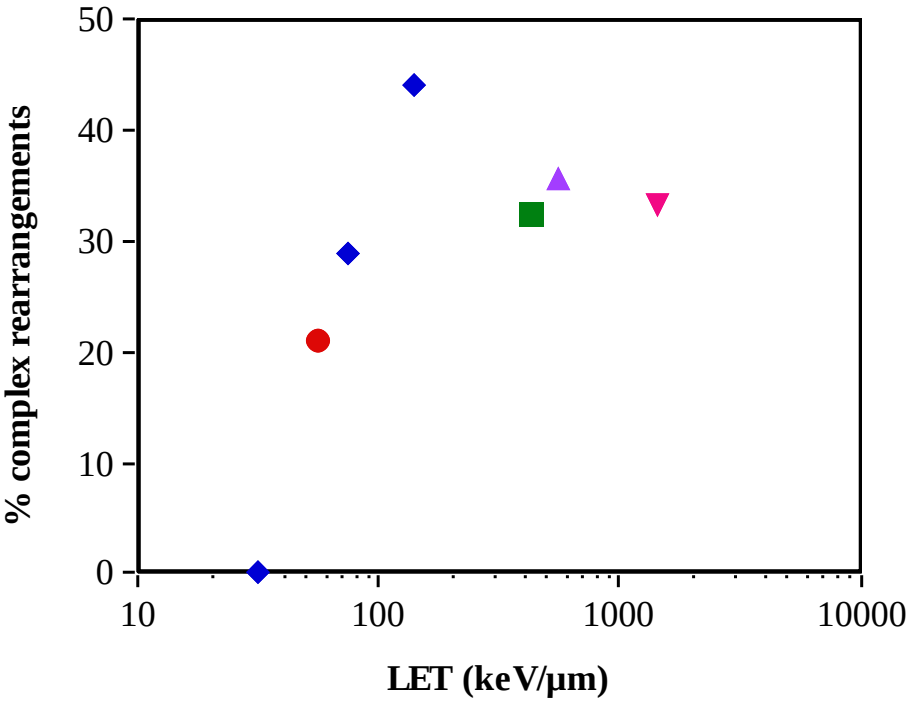
INDUCED BY SINGLE TRAVERSAL OF HIGH LET ION



Low fluence < 1 ion/nucleus

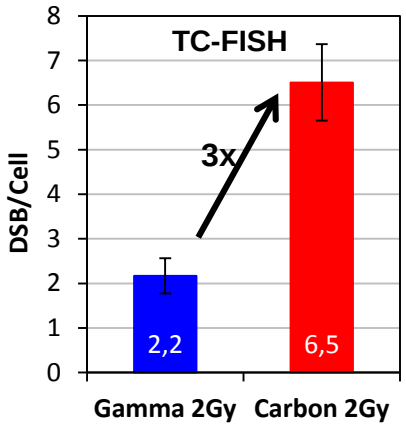
→ **Heavy chromosome damage induced by ion irradiation**

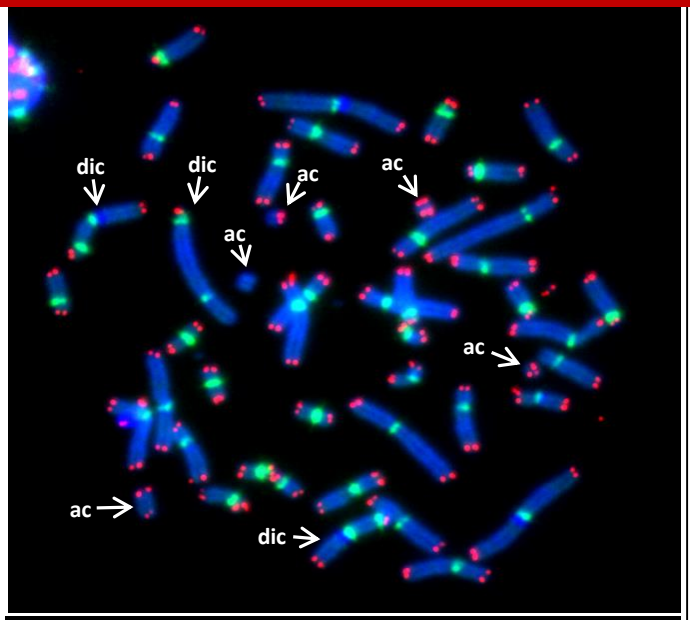
- several breaks involved
- increases with ions fluence and LET
- Crea induced by a single ion (LET ≥ 55 keV/µm)

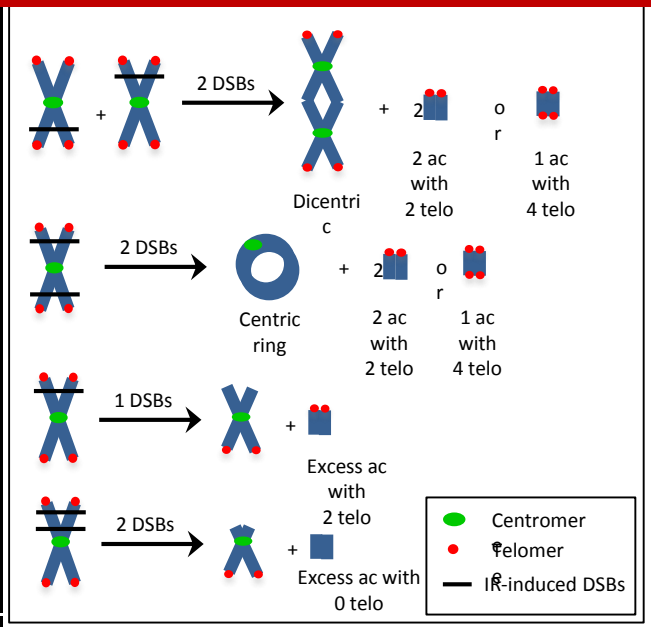


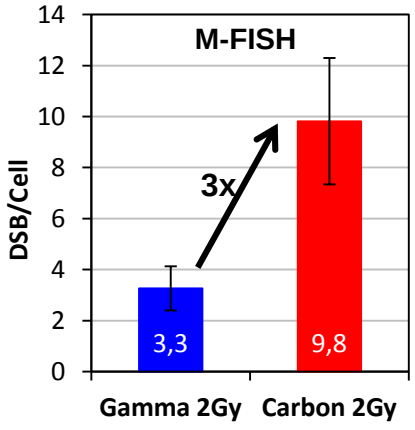
Sabatier et al, 1987, Mut Res
Testard et al, IJRB, 1997

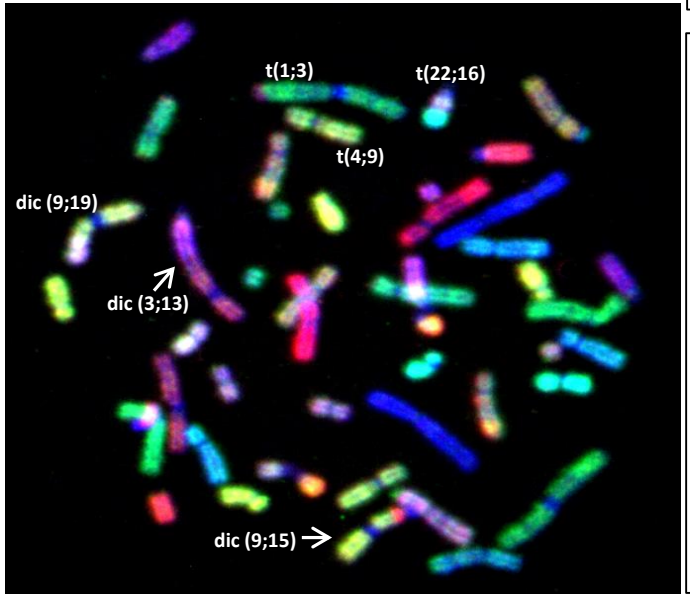
TC-FISH and M-FISH : two alternative approaches for scoring chromosomal damage => same RDE

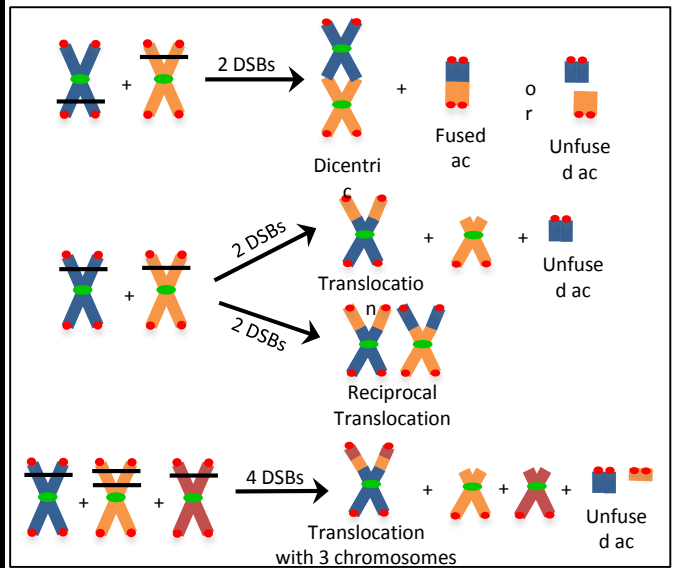










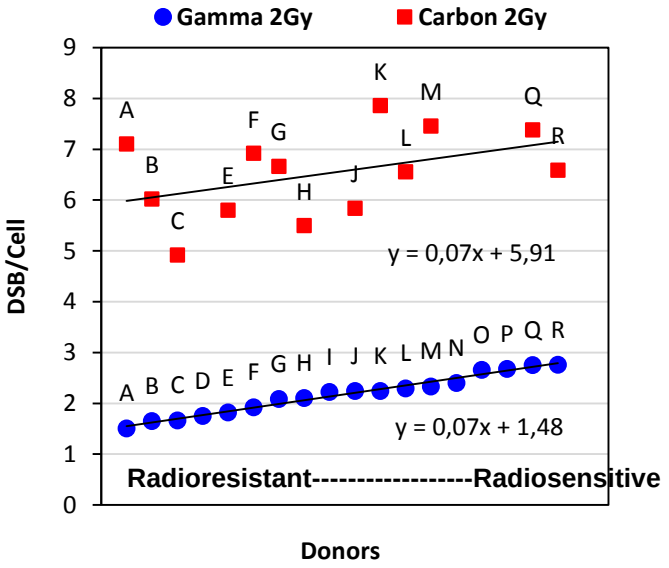


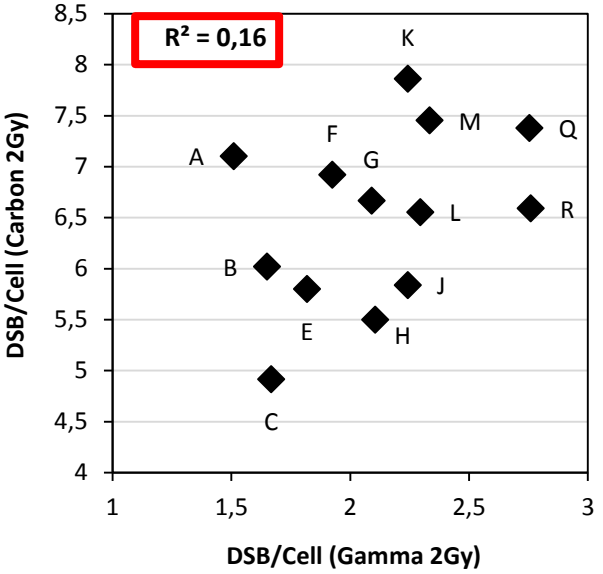
4 donors (Donors A, C, L, R)

Mkacher et al, Mut Res, 2014
Shim G et al. Front in Oncology 2016.

Comparison of individual radiosensitivity to γ-rays and carbon ions

- **No correlations between radiosensitivity to carbon ions and γ-rays at the dose of 2 Gy (R^2 = 0.16)**

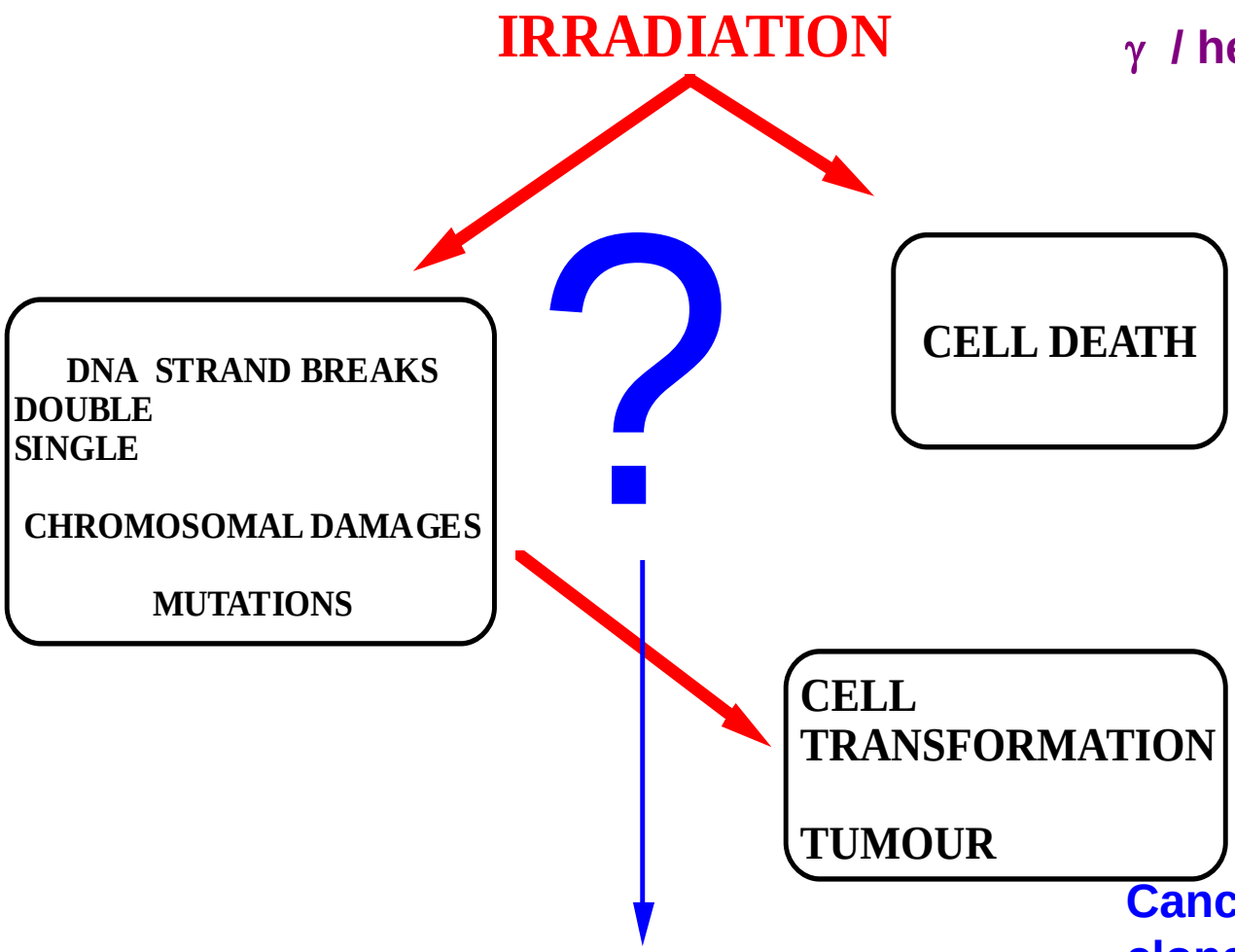




- **These results indicate that donors are not equally sensitive to different types of IR**
- **Type of damages? Repair process?**

Shim G et al. Front in Oncology 2016.

TRANSMISSION OF RADIATION-INDUCED DAMAGES



Cancer cells :
clonal evolution from a single ce
chromosome imbalances
chromosome rearrangements

Mutation Research 760 (2014) 1–17

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Review

Crosstalk between telomere maintenance and radiation effects: A key player in the process of radiation-induced carcinogenesis☆

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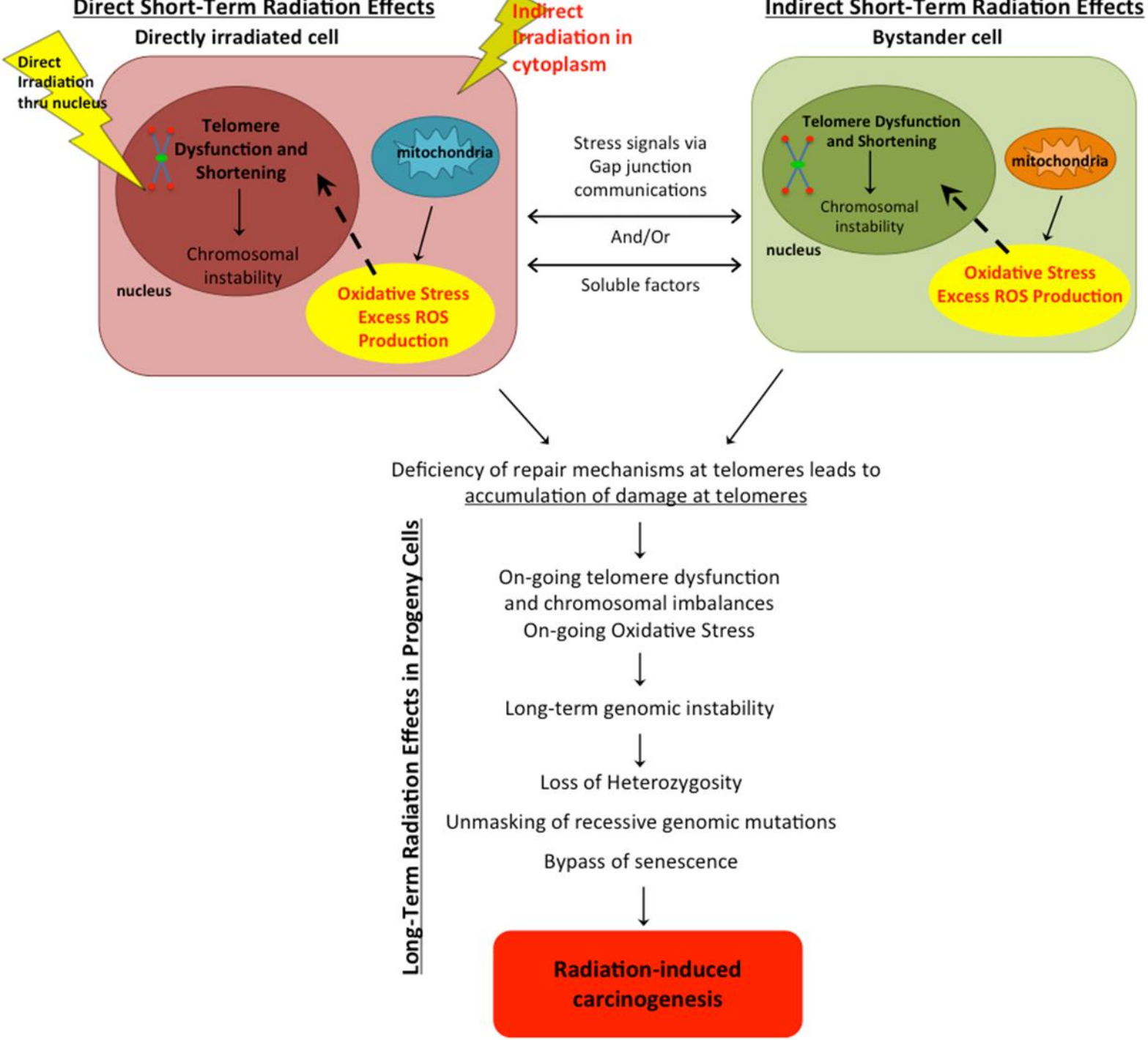
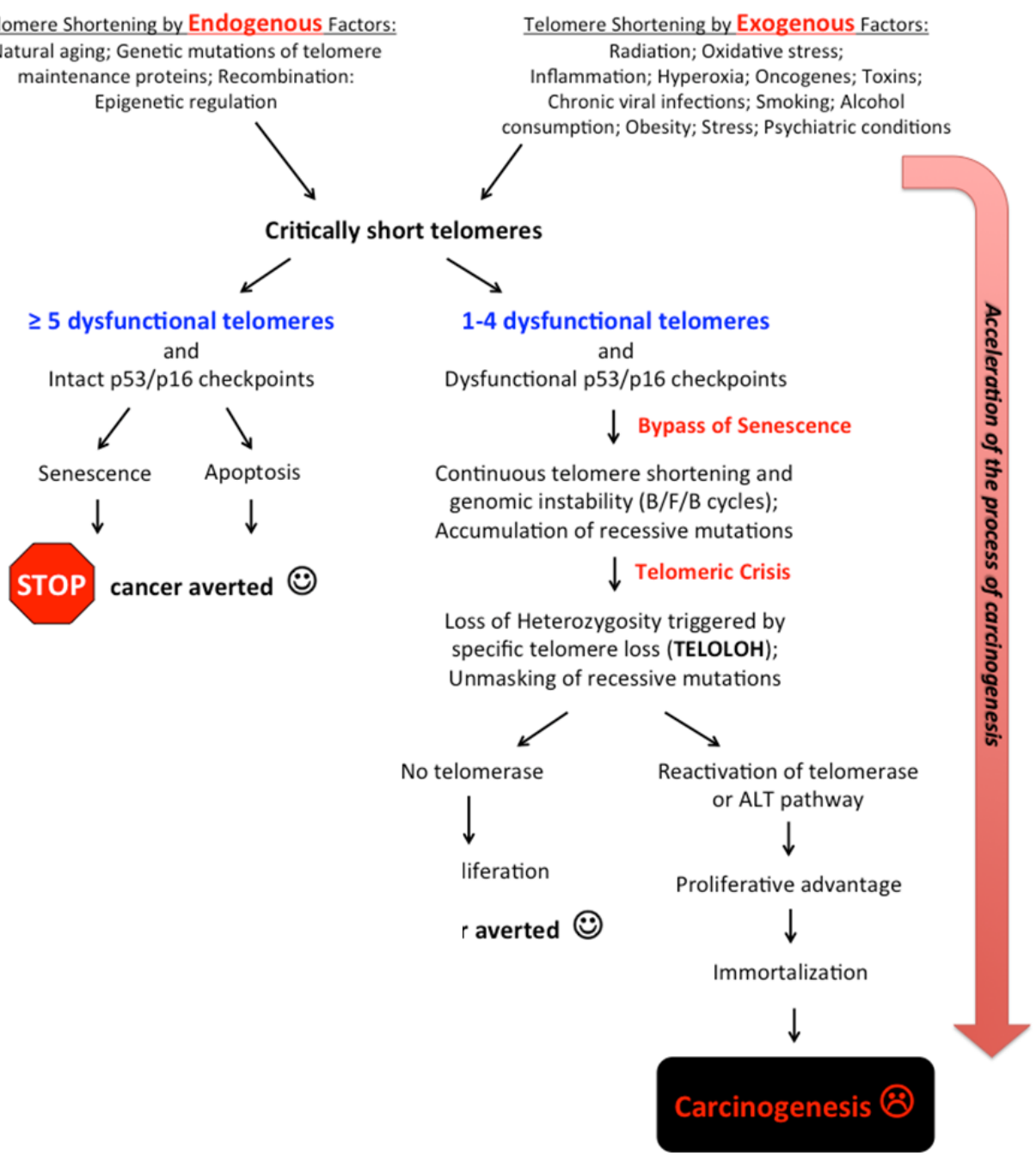


Shim et al, Mut Res, 2014



Shim et al, Mut Res, 2014

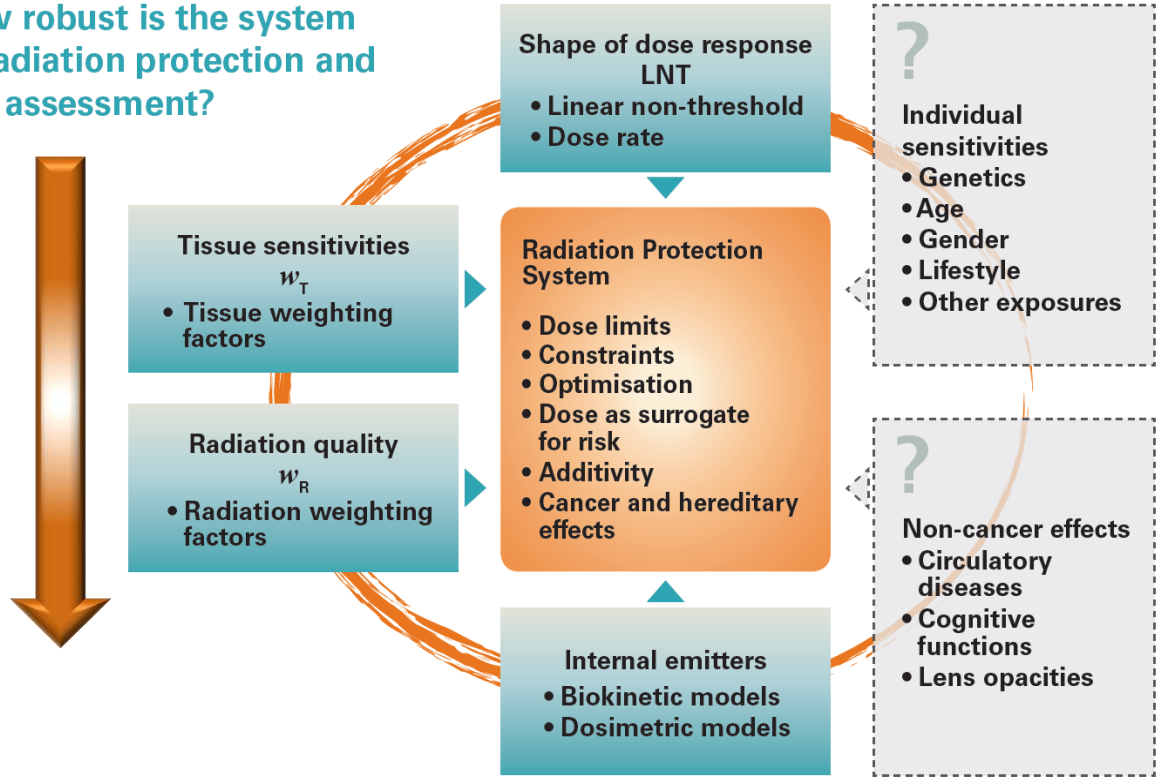
EURATOM / RADIOPROTECTION => INTEGRATION

2006 - 2007 - 2008 - 2009 - 2010 - 2011 - 2012 - 2013 - 2014 - 2015 - 2016 - 2017

FP6 | FP7 | H2020

Risc-Rad

2009
HLEG report



EURATOM / RADIOPROTECTION => INTEGRATION

2006 - 2007 - 2008 - 2009 - 2010 - 2011 - 2012 - 2013 - 2014 - 2015 - 2016 - 2017

FP6 | FP7 | H2020

Risc-Rad

2009
HLEG report

- 2010 : MELODI

« Low doses »

« emergency situations » »

« Radioecology »

« Dosimetry » »

SRA : Strategic Research Agenda

Associations of research institutes
Major aim is to publish Research Agendas and to propose Priorities lists
NO FUNDS

2008 :

- 2009 : NERIS
- 2010 : ALLIANCE

Medical Use

SSH

EC FP6 TO H2020 => INTEGRATION

		FP6 (M€)	FP7 (M€)	H2020
Sub-Areas	Low-dose radiation	27,0	34,7	
	Medical, Radiobiology,Dosimetry	11,4	40,0	
	Emergency Preparedness	7,7	5,9	
	Education & Training	1,1	0,8	
	Radioecology	2,4	7,4	
	Total	49,5	88,7	
	% Fission	27%	25%	20- 30%
Focus	Integration / Joint Programming /Joint Calls (CSA,NoE,CP-IP)	24	45	EJP
	Others (CP-FP, STREP)	26	44	

INTEGRATION APPROACHES AT EUROPEAN LEVEL

FP7 | H2020

LABORATORIES LEVEL

5 M€ + 0,1 M€

2010 - 2011 - 2012 - 2013 - 2014 - 2015

INSTITUTIONS LEVEL

4 M€ + 1,5 M€

2013 - 2014 - 2015 - 2016 - 2017

NATIONS LEVEL

2015 - 2016 - 2017 - 2018 - 2019

European Joint Programme (EJP)

The European Joint Programme (EJP) under Horizon 2020 is a **co-fund action** designed to support coordinated national research and innovation programmes.

The EJP aims at attracting and pooling a critical mass of national resources on objectives and challenges of Horizon 2020 and at achieving significant economies of scales by adding related Horizon 2020 resources to a joint effort.

HORIZON 2020

European Joint Programme

- A new H2020 instrument
  - In pilot phase in EURATOM WP2014-2015.
- Wide variety of activities
  - Internal implementation.
  - Possibility of multiple calls for cascading grants.
- Up to 70% reimbursement rate
  - To be fixed in the Work Programme
- 5 years/5 reporting periods
  - Annual programming and reporting cycle.

EURATOM / RADIOPROTECTION => INTEGRATION

2010 - 2011 - 2012 - 2013 - 2014 - 2015 - 2016 - 2017 - 2018 - 2019 - 2020 -

FP7 | H2020

Projects selected and funded by Euratom Research, Coordination, call for proposals, FUNDING

CONCERT
- European Joint Program: 2015 - 2020

DoReMi (Integrating Low Dose Research)
- Network of excellence : 2010 - 2015

NERIS-TP
- Preparatory actions: 2011 - 2014

OPERA (Open Project for European Radiation Research Area)
- Preparatory actions : 2013 - 2016

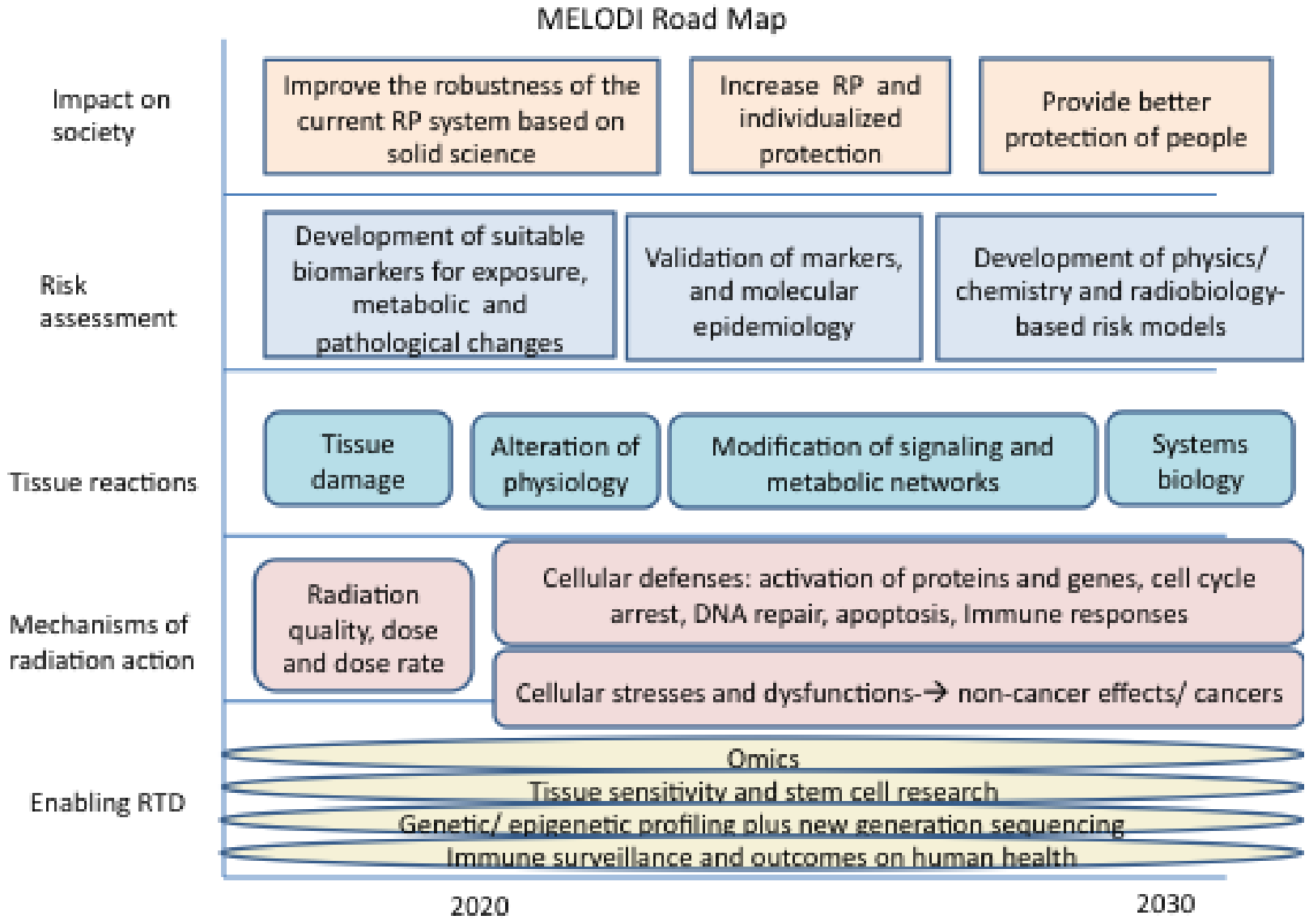
STAR (Strategy for Allied Radioecology)
- Network of excellence : 2011 - 2015

COMET (COordination and iMplementation of a pan European instrumenT for Radioecology)
- Preparatory actions : 2013 - 2016

- « Low doses »
- « emergency situations » »
- « Radioecology »
- « Dosimetry » »
- « Medical Use» »
- « SSH»

MELODI :STRATEGIC RESEARCH AGENDA

▪ 2016



EURATOM / RADIOPROTECTION => INTEGRATION

- 2010 : MELODI

- To understand the potential impact of individual susceptibility on radiation-induced health effects (Rank 1: high priority)
- To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases (Rank 2: medium priority)
- To understand the health effects of inhomogeneous dose distributions, radiation quality and internal emitters (Rank 2: medium priority)
- To explore and define the role of epigenetic modifications in radiation-induced health effects (Rank 2: medium priority)
- To explore the roles of specific target cells for radiation-induced late developing health effects (Rank 2: medium priority)
- To explore the shape of the dose-response relationship for radiation-induced health effects (Rank 3: low priority)

WG SRA
WG Infrastructures
WG Education & Training

MELODI encourages, where appropriate, (1) the use of archived biological materials from prior EU funded research, (2) the integration of experienced laboratory networks (such as e.g. RENEB), (3) the integration of expertise from outside the conventional fields of radiation research, in particular expertise from the medical research field where appropriate.

EURATOM / RADIOPROTECTION => INTEGRATION

- 2010 : ALLIANCE

Two priorities with impact expected mainly in terms of reduced uncertainty in exposure and dose assessment and increased human and wildlife radiation protection:

 Environmental availability and impact of radionuclides in terrestrial and freshwater ecosystems (including human food chain) and their interactions with atmosphere, incorporating physical, chemical and/or biological processes. Validated process-based model parameterisation, characterisation of variability and uncertainty, and guidance for fit-for-purpose models **(ranked as priority 1)**

 Development of models/tools, and datasets for their calibration and validation and guidance to select and evaluate the effectiveness of different remediation strategies in long-lasting exposure situations (*e.g.* nuclear accidents and/or NORM/TeNORM) **(ranked as priority 3)**

Two priorities with impact expected mainly in terms of reduced uncertainty in effect assessment and increased wildlife radiation protection:

 Biomarkers of exposure and effects to living organisms as operational outcomes of a mechanistic understanding of intra- and inter-species variation of radiosensitivity to chronic low dose exposure situations **(ranked as priority 2)**

 Multiple stressors and modulation of radiation effects in living organisms **(ranked as priority 4)**.

The ALLIANCE encourages where relevant openness to other disciplines to integrate their skills and knowledge into radioecology, and capitalisation of best practices, tools and data in the various fields of research needed. Additionally, research combining “lab-field-modelling” approach and fit-for-purpose applications will be appreciated.

EURATOM / RADIOPROTECTION => INTEGRATION

1. To quantify correlations between track structure and radiation damage
2. To improve neutron dosimetry techniques
3. To quantify doses after accidental internal contamination
4. To develop accurate and on-line personal dosimetry for workers
5. To improve the measurement and combination of out-of-field radiotherapy and imaging doses in photon and particle radiotherapy, for input to epidemiological studies
6. To improve dosimetry in modern external beam radiotherapy

EURATOM / RADIOPROTECTION => INTEGRATION

- 2009 : NERIS

1. **Assessment of and communication of uncertainties**.
2. **Robust decision---making.**
3. **Countermeasure strategy preparedness.**
4. **Atmospheric dispersion modelling.**
5. **Local radio---ecological models.**
6. **Monitoring strategies.**

EURATOM / RADIOPROTECTION => INTEGRATION

SRA
- 2017
- EURAMED

1. **Measurement and quantification in the field of medical applications of ionising radiation**
2. **Normal tissue reactions, radiation-induced morbidity and long term health problems.**
3. **Optimisation of radiation exposure and harmonisation of practices**
4. **Justification of the use of ionising radiation in medical practice**
5. **Infrastructures for quality assurance**

EURATOM / RADIOPROTECTION => INTEGRATION

- 2017
- SSH

Research line 1: Effects of social, psychological and economic aspects on radiation protection behaviour and choices of different actors .....

Research line 2: Holistic approaches to governance of radiological risks.....

Research line 3: Guiding principles for Responsible Research and Innovation in Radiation Protection.....

Research line 4: Stakeholder engagement in radiation protection research, development, policy and practice.....

Research line 5: Risk communication.....

Research line 6: Radiation protection culture.....

EJP CONCERT

UMBRELLA STRUCTURE FOR RADIATION PROTECTION RESEARCH IN EUROPE (2015 – 2019)

EUROPEAN JOINT PROGRAMME FOR THE INTEGRATION OF RADIATION PROTECTION RESEARCH
CONCERT

- **Co-funding action**
- **Joint programming**
- **Open research calls**
- **Integrative activities**

- WP 2015.
- 54 partners 32 Project managers (POM). POM

- WP1: Project coordination & management, **BFS** (Allemagne)
- WP2: Integration and SRA development in radiation protection research **STUK** (Finlande)
- WP3: Joint R&D programming **SCK-CN** (Belgique)
- **WP4: Open R&D call preparation, ANR** (France)
- WP5: Stakeholder involvement & communication in RP research, **PHE** (UK)
- **WP6: Access to Infrastructures, CEA** (France)
- WP7: Education and Training , **Uni Pavia** (Italie)

EJP-CONCERT Founding Scheme

CONCERT budget

- Total EJP-CONCERT funding = 27.5 Mill. € (in 5 years)
  - EC funding = max. 19.8 Mill. € (70 %)
  - Co-funding = 8.000.000 € (30%) In kind and/or cash

- 60% for two CONCERT open research calls
  - ✓ First call (3,5 years projects). 10,4 M€ (7,3 M€ EC).
  - ✓ Second call (2,5 years projects). 6,8 M€ (4,7 M€ EC).
- 30% for CONCERT integrative activities (joint programming, stakeholder engagement, access to research infrastructure, E&T etc.)
  - **Education and Training: Annual Calls (short courses 1-3 weeks)**
    - **2.3 Mill. €** (EC share: 1.6 Mill. €)
  - **Access to infrastructure**
    - **1.1 Mill. €** (EC share: 0.7 Mill. €)
- 10% for administration and management.

EJP CONCERT : 1ST CALL PRIORITIES (

Scientific priorities responding to society's concerns

	Impact on human health of exposure to ionizing radiation at low doses/ low dose rates	Environment, emergencies and long lasting exposure situations to radioactive substances
Cross cutting issues: Social Science and Humanities (SSH) Basic safety standards (BSS) Infrastructure Education & Training (E&T)	Improving knowledge on the shape of the dose-response-relationship for radiation-induced health effects at low doses/ dose rates, including all relevant dose components and dose uncertainties and fundamental considerations of radiation tracks at molecular and cellular levels, to strengthen the scientific base for radiation protection	Improving the consideration of uncertainties in human and ecosystem radiological risk assessment including appropriate exposure quantification, and in risk management of nuclear emergencies and existing exposure situations including NORM, for enhanced decision making

EJP CONCERT : 2 nd CALL PRIORITIES

Topic 1 Understanding human health effects from ionising radiation and improving dosimetry

Sub-topics:

I. Improvement of health risk assessment associated with low dose/dose rate radiation

II. Improvement of occupational dosimetry

III. Patient-tailored diagnosis and treatment: full exploitation and improvement of technology and techniques with clinical and dose structured reporting

Topic 2 Radioecology, emergency and social sciences and humanities

Sub-topics:

I. Biomarkers of exposure and effects in living organisms, as operational outcomes of a mechanistic understanding of intra- and inter-species variation of radiosensitivity under chronic low dose exposure situations

II. Countermeasure strategies preparedness for emergency and recovery situations

III. Models, tools and rationales for stakeholder engagement and informed decisionmaking in radiation protection research, policy and practice for situations involving exposures to ionising radiations.

RADIOBIOLOGY PRIORITIES

Radiation protection

Public

Medical use

Occupational
Earth Space

Shared priorities

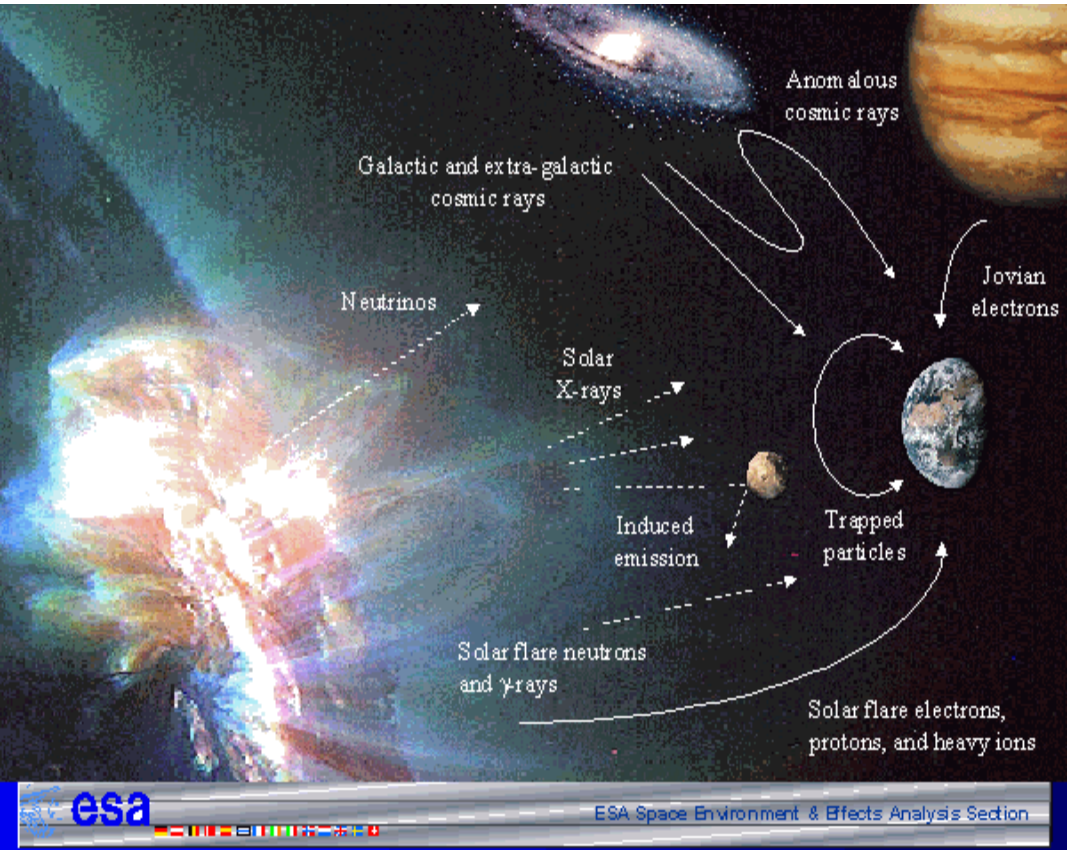
CHALLENGES / SPACE RADIOBIOLOGY

Area	Topic	Subtopics	Practical impact in space	European competence
Cancer risk	Molecular mechanisms of carcinogenesis by charged particles	DNA repair Genomic instability Epigenetic changes Non-targeted effects	High impact for risk assessment. Low impact for mission criticality	Concentrates on low dose low LET
	Innovative experimental models for cancer risk assessment at low doses and low dose rates	1. Animal and tissue models 2. 3D cultures 3. Specific models for leukaemia and breast, thyroid, colon, and lung cancers	High if accompanied by appropriate modeling to translate in accurate risk coefficients	Good
	Individual susceptibility and biomarkers of risk	1. Genes or proteins responsible for radiosensitivity 2. New methods in biodosimetry	Potentially high for prevention and intervention	Good
Noncancer risk	Accelerated aging induced by energetic charged particles	1. In vitro senescence mechanisms 2. Development of animal models 3. Extrapolation to risk of cardiovascular diseases	High impact for risk assessment. Low impact for mission criticality	Good
	CNS damage	Behavioral endpoints Molecular studies	High for a go/no-go decision	Good
Acute effects	Risk of radiation sickness induced by very intense SPE	1. Simulations of SPE 2. Prodromal syndrome for protons at low dose rate	Very high for mission criticality	Excellent from radiotherapy
Hereditary risk	Risk of transgenerational genetic alterations induced by cosmic radiation	1. RBE of heavy ions for the induction of hereditary damage 2. Combined effects of radiation and other stressors on reproduction in space	Especially relevant for future human colonization of space. Impact on pregnancy planning of astronauts	Excellent
Combined effects	Interaction between space environment and radiation	1. Bioreactors to simulate ìg on ground 2. Effect of stress on radiation response (adaptation, sensitization?) 3. Radiation and stressors on planetary surfaces	Potentially high for prevention/ intervention if protection or enhancement is proven	Excellent in stress response and flight experiments
	Mixed radiation fields	1. Simultaneous high-/low-LET radiation exposures 2. Effect of pre-exposure to low dose rate protons on response to single heavy ions 3. Biophysical modeling of mixed radiation fields	Potentially high if adaptive response or synergism is proven	Excellent
Counter measures	Shielding	1. Nuclear fragmentation 2. Material testing 3. Biological effects and shielding	Very high for the spacecraft and habitat modules design	Good
	Radioprotectors	1. Drugs to prevent acute radiation sickness 2. New molecules to decrease late morbidity	High to mitigate SPE risk	Good from radiotherapy
	Dietary supplements	1. Antioxidants as radioprotectors 2. Tests with heavy ions, low dose rates, and different endpoints	High for prevention	Good

GROUND-BASED STUDIES => INFRASTRUCTURES

- Particles trapped in Earth magnetic fields : Van Allen belts (electrons, protons = H 600 MeV, few ions)
- Solar radiation : neutrons, γ, protons, α particles and ions (E -> 1 GeV)
- Cosmic and galactic rays : 2% electrons and positrons

  98% particles : - 87% protons
  - 12% alphas
  - 1% heavier ions



Ions are ~1% of the radiations but can represent up to 50% of the total dose

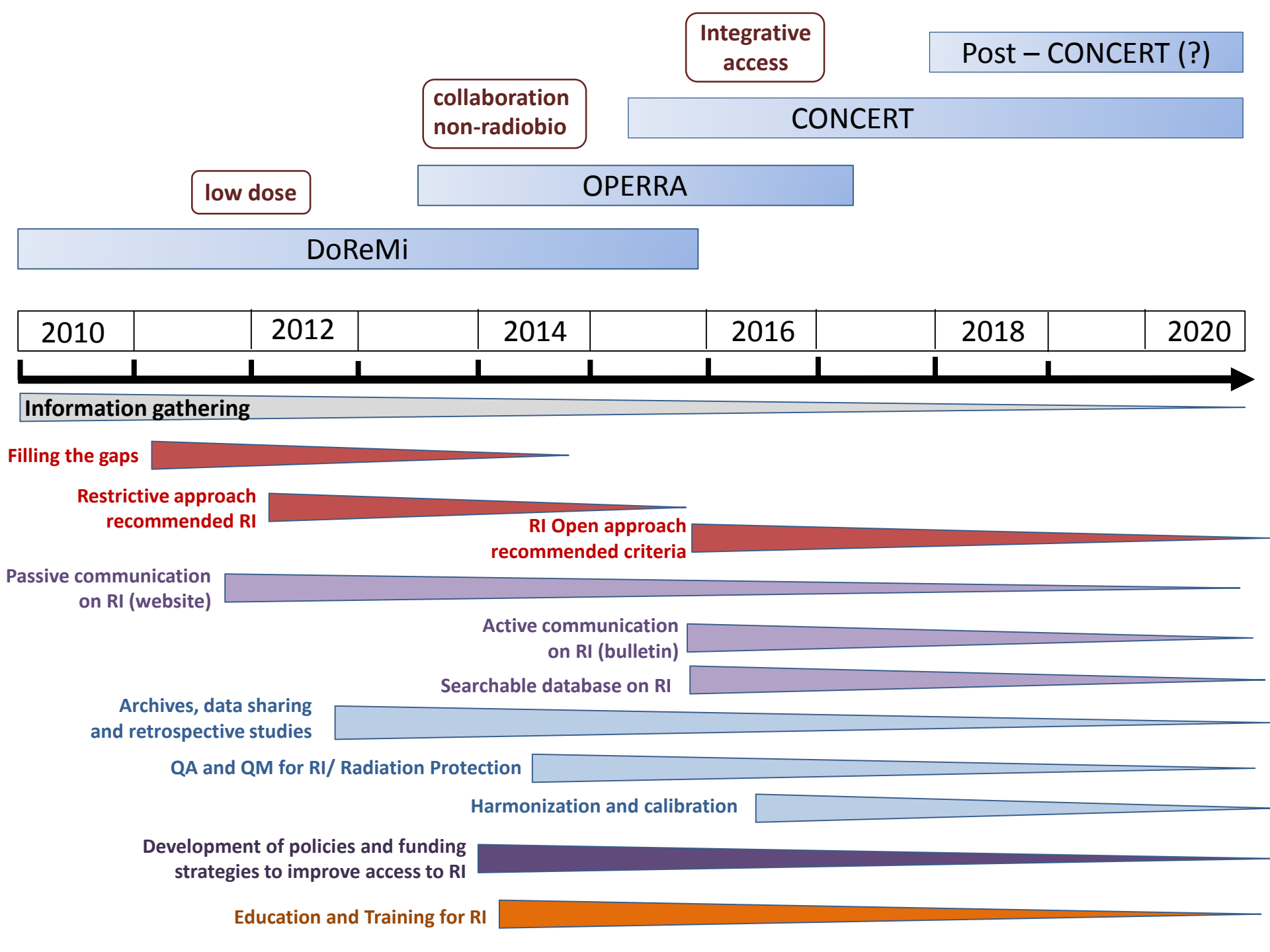
↳Increased risk of biological damage for long-term flights (Mars > 1% cells hit)

GROUND-BASED STUDIES => INFRASTRUCTURES

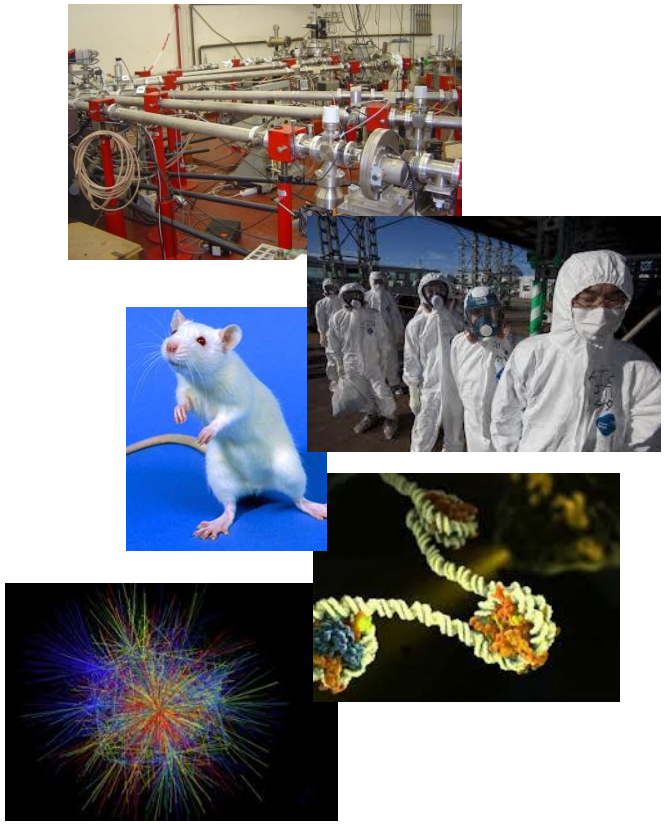
Facility name location / country	Species	Energies
GSI (SIS18)* Darmstadt / Germany	All	70 - 1000 MeV/u (see table 3 above)
AGOR KVI-CART Groningen / Netherlands	All	Protons (190 MeV) ^{3}He (120 MeV/u) ^{4}He, ^{12}C, ^{16}O (90 MeV/u) ^{20}Ne (75 MeV/u) Heavier ions available (full list at http://www.rug.nl/kvi-cart/)
GANIL Caen / France	All	Neutrons Protons (33 MeV) ^{56}Fe (71 MeV/u) All ions are available (full list at http://pro.ganil-spiral2.eu/users-guide/accelerators)
MedAustron Wiener Neustadt / Austria	H … C	E_{max}: 400 MeV/u (protons: 800 MeV/u)
Institute Curie (CPO) Orsay / France	H	230 MeV

Facility name location / country	Species	Energies
Centre Antoine Lacassagne (CAL) Nice / France	H	Protons (230 MeV) Deuteron (29 MeV)
RPTC Munich / Germany	H	E_{max}: 250 MeV
HIT Heidelberg / Germany	H, He, C ,O	^{12}C: 80-430 MeV/u ^{16}O: 103-430 MeV/u ^{4}He: 50-220 MeV/u Prot.: 50-220 MeV/u
MIT Marburg / Germany	H ,C	^{12}C: 70-430 MeV/u Prot.: 50-225 MeV/u
WPE Essen / Germany	H	70- 230 MeV
PTC Dresden / Germany	H	70 - 230 MeV
CNAO Pavia / Italy	H, C (He, O)	H: 63 -230 MeV ^{12}C: 115 – 400 MeV/u (other species available soon)

Facility name location / country	Species	Energies
Trento Proton Therapy Center - TIFPA Trento / Italy	H	70 – 228 MeV
LNS – INFN Catania / Italy	All	Proton (80 MeV) H, He, Li, Be, B, C, Ne (between 45 and 80 MeV/u) and heavier ions up to Au (between 10 and 50 MeV/u) (full list at https://www.lns.infn.it/it/)
PSI Villingen / Switzerland	H	E_{max}: 250 MeV


Integrative access
Post – CONCERT (?)
collaboration non-radiobio
CONCERT
low dose
OPERRA
DoReMi
2010
2012
2014
2016
2018
2020
Information gathering
Filling the gaps
Restrictive approach recommended RI
RI Open approach recommended criteria
Passive communication on RI (website)
Active communication on RI (bulletin)
Searchable database on RI
Archives, data sharing and retrospective studies
QA and QM for RI/ Radiation Protection
Harmonization and calibration
Development of policies and funding strategies to improve access to RI
Education and Training for RI

- Exposure platforms
- Databases, sample bank and cohorts
- Analytical platforms models and tools



Improve visibility

AIR² Bulletin

AIR² Access to INFRASTRUCTURES for Radiation protection Research

Issue 20
September 2017

Editorial

The results of the 2nd CONCERT Call are beginning to emerge. The success of this call has been remarkable! Although the budget allocated was less than for the 1st call (€6.98 million *vs* €10.4 million), twice as many proposals were received (24 *vs* 12). We now know the 6 projects selected: 4 are from topic 1 (Understanding human health effects from ionising radiation and improving dosimetry) (20 projects submitted), and 2 are from topic 2 (Radioecology, Emergency and SSH) (4 projects submitted). The financial distribution between the two calls has now rebalanced, with 80% of the budget from the 2nd Call being allocated to topic 1.

Again, only the acronyms and project titles were whispered to us, and not the infrastructures needed.

Dr Laure Sabatier, CEA

The floor to...

In the last few months, many of you may have found different messages in your inbox underlining the importance of research data and open access. In June, Springer Nature launched a survey on how we manage research data. In May, the European Commission contacted beneficiaries to inform them of the open access obligations in Horizon 2020. And we, in CONCERT Subtask 6.2.2, also invited researchers in the radiation protection field to take part in our survey on data management. The main goals of the survey were to find out why researchers were not sharing their data and what kind of support would be effective to populate databases with past and ongoing studies, which is the main objective of this subtask.

Incrementing Databases
With past and on-going studies

The survey was sent to the members of the CONCERT-all mailing list, asking them to distribute it extensively. The results showed that 44% of respondents had not heard of the STORE database. This is quite surprising if we consider that the survey participants all have some links with the CONCERT project. The survey also revealed that the participants had limited awareness of their IPR rights in relation to raw data.

The lack of time available to make data understandable is another major barrier. Based on the survey, specific funding or internal assistance for data sharing can be an effective means of support for researchers. However, it was also found that requirements set by funding bodies to make public data sharing obligatory is another effective approach because most participants fully concur with the requirements of their funding bodies, institutions or journals.

While it is not clear whether the funding of data sharing is possible within the CONCERT project, we have to work hard to increase the visibility of data sharing infrastructures and to provide information about open data policies and the rights related to raw data. We are looking forward to seeing the first data generated in CONCERT-funded projects and uploaded to STORE. As one respondent wrote, "Sharing data should be the MUST for the future of research". We hope that these actions will help to establish a data sharing culture in radiation protection research that will bring this future closer.

Dr Balasz Madas
MTA-EK
CONCERT WP 6.2.2

Photo: Borbála Madas

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

CONCERT CORNER

Future events:

October 9th 2017:
ExB/ESAB: 13h00 - 14h30
MB: 15h00 - 17h00

WP 6 News:

Next WP6 meeting:
October 10th, Paris, France
During the ICRP-ERPW

AIR²D²:
- Please complete the online form(s) to register your infra-structure(s) in the database.
- A new option to feature your infrastructure is now available: add document.

Contents:

Next issue

October 2017

Published to date:

Issue	Exposure platforms	Databases, Sample banks, Cohorts	Analytical platforms, Models & Tools
Oct 2015, #1	FIGARO	FREDERICA	RENEB
Nov 2015, #2	B3, Animal Contamination Facility	The Wismut Cohort and Biobank	The Hungarian Genomics Research Network METABOHUB
Dec 2015, #3	Pulex Cosmic Silence	STORE	
Feb 2016, #4	SNAKE	French Haemangioma Cohort and Biobank	Dose Estimate, CABAS, NETA
Mar 2016, #5	Radon exposure chamber	3-Generations exposure study	PROFI
Apr 2016, #6	Biological Irradiation Facility	Wildlife TransferDatabase	Radiobiology and Immunology platform (CTU-FBMF)
May2016, #7	CIRIL	Portuguese Thyroid Cancers Cohort	LDRadStatsNet
Jun 2016, #8	Mixed alpha and X-ray exposure facility	Elfe Cohort	ERICA Tool
Jul 2016, #9	SCRS-GIG	RES²T	CROM-R
Sep 2016, #10	Facility radionuclides availability, transfer and migration	INWORKS cohort	France Génomique
Oct 2016 #11	LIRIS gamma low dose rate facility ISS	JANUS	Transcriptomics platform SCKCEN
Nov 2016, #12	Microtron laboratory	EPI-CT Scan cohort	CATI
Dec 2016, #13	Nanoparticle Inhalation Facility	LIEF Biobanking	The Analytical Platform of the PRP-PARE project
Feb 2017, #14	Infrastructure for retrospective radon & thoron dosimetry	Chernobyl Tissue Bank	HZDR Radioanalytical Laboratories
Mar 2017, #15	Alpha Particles Irradiator Calibration Laboratory at KIT		SYMBIOSE
Apr 2017, #16	Changing Dose rate (SU) Low dose rate (SU)		Advanced Technologies Network Center
May 2017, #17	Chernobyl Exclusion Zone	Chernobyl clean-up workers from Latvia	IRS whole and partial body Counting
Jun 2017, #18	MELAE	Belgian Soil Collection	INERAFONTIER
Jul 2017, #19	MICADO'LAB	Fatcham Cohort	ECORITME
Sep 2017, #20	DOS NDS		CERES
Oct 2017, #21	To Be Announced	To Be Announced	To Be Announced

40 issues
120 Infrastructures
Web handbook

Editorial Committee: Jean-Michel Dolo, Maria Panagiotopoulou, Elisabeth May, Laure Sabatier

Future events:

CONCERT Short Courses

30 October-10 November 2017

Molecular Mechanisms of Radiation Carcinogenis
IHelmholtz Center - Munich Institute for Radiation Biology, Germany

Contact:
Michael Rosemann
Rosemann@Helmholtz-muenchen.de

5-9 February 2018

Emergency and recovery preparedness and response
National Center of Radiobiology and Radiation Protection, Bulgaria

Contact:
Nina Chobanova
n.chobanova@ncrrp.org

19-23 February 2018

Radiation Protection:
Basics and Applications

Forschungszentrum Jülich, Germany

Contact:
Ralf Kriehuber
r.kriehuber@fz-juelich.de

Other Events

3-8 September 2017

ICRER 2017, 4th International conference on Radioecology and Environmental Radioactivity,

Berlin, Germany

10-12 October 2017

Joint ICRP-RPW 2017

Paris, France

24-25 October 2017

International Workshop on the INEX 1 exercises

OECD Nuclear Energy Agency Boulogne-Billancourt, France

5-11 November 2017

MICROS 2017, 17th International Symposium on Microdosimetry, Venice, Italy

See also on CONCERT website

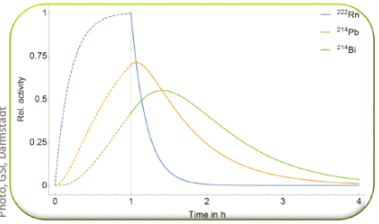
Exposure platforms

Radon Exposure Chamber

Investigating anti-inflammatory effects of ionizing radiation

Radon is used in the treatment of chronic inflammatory diseases such as rheumatoid arthritis or ankylosing spondylitis. Patients are subjected to radon baths or inhalation therapies in radon galleries. Within the GREWIS project, eight scientific groups at GSI, TU Darmstadt and the Universities of Frankfurt and Erlangen are currently investigating the underlying physical and biochemical mechanisms and the genetic effects potentially linked to low dose radon exposure.

At GSI, a radon chamber was constructed to mimick stable radon gallery conditions and up to 15 times higher radon concentrations. The complete chamber is positioned in a radiologically controlled area. In adjacent biological laboratories, experiments can be performed with cell cultures and small animals such as mice. The exposure chamber has a volume of 50 litres allowing the exposure of up to 15 mice or 24 petri dishes (diameter: 5.5 cm). During experiments, the samples are exposed to radon-222 and its short lived daughters. The gas accumulates in a radium-226 source and is flushed into the experiment chamber. By varying the accumulation time, it is possible to adjust the radon concentration. The dose depends on the activity-concentration and the exposure time and is usually in the µGy range. During the experiments, the system operates as a closed circuit. Before removing the samples from the chamber, it is flushed with air to dilute and wash out the radon, which is collected in an activated coal filter.



Photo, GSI, Darmstadt

Relative activity of the primary Rn-222 and the daughter nuclei Pb-214 and Bi-214 over time taking radioactive decay and diffusion into account

The chamber is mounted in a heated water bath with an integrated thermostat, which enables the temperature to be controlled with high accuracy and stability. In addition, the relative humidity is controlled using a carrier gas mixed with vaporized sterile water to avoid biological contamination. For cell culture experiments, additional CO_2 regulation can be used which is deactivated for animal experiments. A summary of the different parameters and their limiting values is illustrated in the table below.


Photo: G. Otto/GSI, Darmstadt

A. Maier, G. Kraft, C. Fournier

After an intense test phase, the radon chamber was used to expose mice in therapy-like conditions, and biological tissue up to the highest possible concentration. In the mice experiments, the local exposure of radon was detected using a marker for DNA damage (double strand breaks) in various tissues. Tissue samples such as fat, bone and tendon from commercially available pork meat were used for the first measurements. These revealed that primary radon diffuses out of the tissue within a few minutes after exposure and that the residual radioactivity originates from the daughter nuclei. The amount of the primary radon in the tissue sample could be calculated from the measurement of the gamma activity of lead and bismuth using a sensitive intrinsic Ge detector. A new mobile detector system has been established that will enable in situ measurements to be performed at the radon therapy locations.

Parameter	Range
Activity concentration	0-620 kBq/m³
Temperature	20-37°C
Relative humidity	0-100%
CO_2-concentration	0-20% (only during cell experiments)

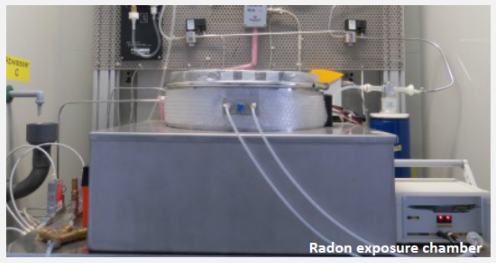


Photo: E. Theenes/GSI, Darmstadt

Radon exposure chamber

GSI

ID Card:

Exposure type:
External (cell culture)
External/Internal (mice)

Source:
Radon-222

Dose rate:
To be determined according to the radon activity concentration, the biological half-life and the duration of the exposure

Irradiation type:
Alpha (5.5 MeV, 6.0 MeV, 7.7 MeV)

Irradiated organism type:
Cells, animals (e.g. mice)

Address:
GSI Helmholtzcenter for Heavy Ion Research, Planckstraße 1, 64291 Darmstadt, Germany

Access:
Registration for cell experiments; animal experiments need to be licensed by local authorities

Supporting lab:
Biochemistry lab, cell culture lab, microscopy, FACS

Internet link:
www.gsi.de/en/work/research/biophysics.htm

Contact:
Claudia Fournier, c.fournier@gsi.de, +49 6159 71 2106
Andreas Maier, a.maier@gsi.de, +49 6159 71 2585

Related to:
MELODI, EURADOS, ALLIANCE

EXPERIMENTAL SETUP FOR RADON EXPOSURE AND FIRST DIFFUSION STUDIES USING GAMMA SPECTROSCOPY. A. Maier et al., Nucl. Instr. Meth. Phys. B 2015, 326: 187-193

RADON EXPOSURE SETUP FOR CELLS AND SMALL ANIMALS. A. Maier et al. GSI Scientific Report 2013, p. 247

Issue 5
March 2016

Databases, Biobanks, Cohorts

FREDERICA

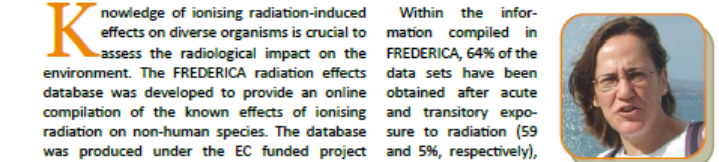
A unique database on the effects of ionising radiation in non-human biota

Knowledge of ionising radiation-induced effects on diverse organisms is crucial to assess the radiological impact on the environment. The FREDERICA radiation effects database was developed to provide an online compilation of the known effects of ionising radiation on non-human species. The database was produced under the EC funded project ERICA (Environmental Risk from Ionising Contaminants: Assessment and Management) and is available online (see link in ID Card).

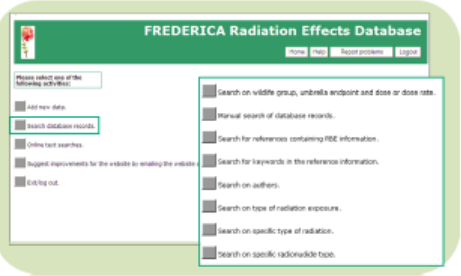
FREDERICA contains some 30,000 data entries from 1,231 references. The data entries correspond to pairs of points (exposure level, biological effect) along with information on the conditions in which these data were obtained (tested species, life stage, exposure regime, effect endpoint, etc.). The data are organised into wildlife groups (amphibians, aquatic invertebrates, aquatic plants, bacteria, birds, crustaceans, fish, fungi, insects, mammals, molluscs, mosses/lichens, reptiles, soil fauna, terrestrial plants and zooplankton). While the biological effects reported in the database are at an individual level, the endpoints considered include those relevant to possible responses at the population level (e.g. reproductive capacity, mortality, morbidity and mutations) [1].

Each reference in FREDERICA was reviewed for the information that is available to the reader in relation to dosimetry, experimental design and statistics. The information provided was scored to reflect the presence or absence of these key data. This provides a measure of the quality of the information in each reference so that if further work is needed (e.g. to refine risk assessment criteria) those papers which contain most, if not all, of the likely information can be easily found.

Within the information compiled in FREDERICA, 64% of the data sets have been obtained after acute and transitory exposure to radiation (59 and 5%, respectively), whereas 36% of the data sets have been obtained after chronic irradiation. Chronic irradiation studies are considered to be more relevant to environmental radiological protection [2]. Considering chronic exposure data, fish, mammals and terrestrial plants are the wildlife groups most widely reported, representing 70.5% of the FREDERICA data for chronic irradiation. The information is scarce for bacteria, crustaceans, fungi, moss and lichen, and zooplankton, since only one or two references have been found for these groups. There is no information on the effects of chronic irradiation for amphibians, aquatic plants or reptiles [1].



Almudena Real

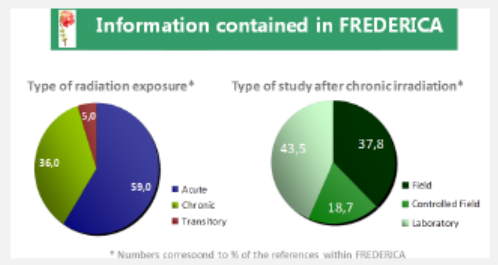


Search capabilities of the FREDERICA database

FREDERICA offers several search capabilities (see Figure above), for which outputs can be exported as an Excel or text file.

The FREDERICA database has been used in many applications, such as:

- Helping define biological effect levels.
- Inclusion as part of the ICRP Reference Animals and Plants (RAPs) review.
- Inclusion as part of the UNSCEAR review on biological Endpoints.
- Integration into the ERICA Tool to perform environmental risk assessments.



FREDERICA Radiation Effects Database

ID Card:

Database topic:
Ionising radiation-induced effects

Information available type:
Exposure-biological effect, species, life stage, irradiation regime. Searchable

Data type:
Peer reviewed articles

Link with a biobank:
No

Exportable:
Yes

Species:
Non-human animals and plants

Internet link:
http://www.frederica-online.org/mainpage.asp

Access:
Free (user needs to register)

Contact:
Almudena Real: almudena.real@ciemat.es; +34 913 466 750
David Copplestone: david.copplestone@stir.ac.uk; +44 01786 467852

[1] THE DEVELOPMENT AND PURPOSE OF THE FREDERICA RADIATION EFFECTS DATABASE. D. Copplestone, et al. Journal of Environmental Radioactivity 99: 1456-1463 (2008).

[2] ISSUES AND PRACTICES IN THE USE OF EFFECTS DATA FROM FREDERICA IN THE ERICA INTEGRATED APPROACH. J. Garnier-Laplace, et al. Journal of Environmental Radioactivity 99: 1474–1483 (2008).

Issue 1
October 2015

Exposure platforms

CIRIL

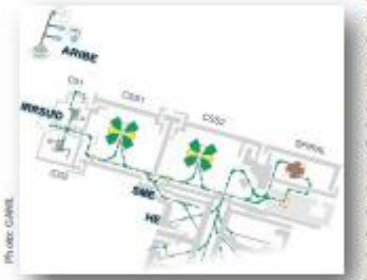
Centre for Interdisciplinary Research with Heavy Ions

The heavy ions accelerated at the GANIL facility (Caen, France) interest not only nuclear, atomic or solid state physics but are also a valuable tool for various studies in radiobiology. The GANIL accelerator can provide various beams, from carbon to uranium, at maximum energies ranging from 95 MeV/A for light ions down to 24 MeV/A for uranium. GANIL cyclotrons supply a wide range of energy, which can be extended further by beam degraders. For the last 20 years, the CIMAP laboratory has managed the CIRIL platform lab user facility for interdisciplinary research at GANIL, which was reinforced 15 years ago by the radiation-biology laboratory LARIA. The biology platform operated by LARIA includes a comprehensive tissue culture room, a molecular biology laboratory and a proteomics laboratory, allowing hosted teams to perform various canonical assays in the radiation biology field. Furthermore, the platform can be adapted for special requirements. The automatic biological sample holder designed at CIMAP can be used with 12.5 and 25 cm^2 flasks, tubes (0.5 ; 1.5 ; 2 and 15 ml), lab-tek™ chamber slide, 8 cm^2 culture dishes and 96-well plates (36 wells irradiated). Fields of interest for platform users are either radiation protection of space travelers (healthy tissues) or cancer treatment (tumours and surrounding healthy tissues). The CIRIL staff consists of the scientific coordinators, the technical coordinators of the four beam lines devoted to interdisciplinary research, the CIMAP technical staff, the physicists of AMA and MADIR, and the radiation-biologists of the LARIA groups who serve as local contacts or beamline scientists for external users.

F. Durantel - Y. Saintigny

Most biology ion exposures are currently performed in the D1 experimental area through the high energy (HE) beam line IRABAT and soon through the medium energy (SME) beam line IRASME. Thanks to the CIMAP expertise in ion irradiation, specific on-line instrumentation has been developed, such as the multi-sample irradiation holder (remotely controlled), beam control software and low dose on-line dosimetry. Most importantly, for each experiment, a team of physicists participates in the beam tuning and dosimetry. This activity has been the initial step to larger local projects linked to the development of hadron-therapy in France (Archade). Most irradiation for biological experiments is done at low dose/fluence (<10 Gy, 10^5-10^7 particles/cm^2). Moreover, studies are focused on ion distribution in adherent cells or 3D models. Providing accurate dosimetry is thus a crucial point for these kinds of experiments.

All the interdisciplinary experiments performed at GANIL have to be evaluated by an international and independent scientific committee (iPAC), even those proposed by CIMAP researchers. Each year, more than 25 UT (25 x 8 hours) of beam time are allocated to the radiation-biology programme by iPAC.



Pictures: GANIL

The 4 beamlines for the interdisciplinary researches corresponding to 4 exits at different locations on the ion accelator. ARIBE is located outside the GANIL INB, whereas IRRSUD, SME and HE are inside the INB on the GANIL facility.

Automatic biological sample holder designed at CIMAP

Photos: F. Durantel, LARIA-PFCM

ID Card:

Exposure type:
External exposition

Source:
Cyclotrons

Dose rate:
0.3 to 3 Gy/min

Irradiation type:
Accelerated ions beam (^{12}C to ^{238}Pb). Horizontal

Irradiated organism type:
Cells (2D and 3D models)

Address:
GANIL – CIMAP, Bd Henri Becquerel, 14070 Caen, France

Access:
Selection committee (iPAC)

Supporting lab:
Radiation biology platform with cell culture lab, biomolecular and biochemistry lab.

Internet link:
http://cimap.ensicaen.fr/spip.php?rubrique138

Contact:
Florent Durantel, durantel@ganil.fr;
ciril@ganil.fr

Yannick Saintigny, saintigny@ganil.fr

Related to:
MELODI, ALLIANCE, EURADOS

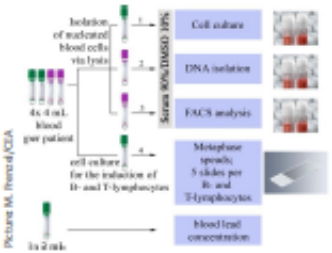
OSIMETRY FOR RADIOBIOLOGY EXPERIMENTS AT GANIL. Durantel et al. NIM A. 2016.
CTIVATION OF THE NUCLEAR FACTOR KB PATHWAY BY HEAVY ION BEAMS OF DIFFERENT LINEAR ENERGY TRANSFER.
elweg et al. Int. J. Radiat. Biol., vol. 87, no. 9, pp. 954–963, Sep. 2011.

Databases, Sample banks, Cohorts

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.

Photos: Hartmann Schreiber

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.

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)

Contacts:
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Dr Laure Sabatier
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+33 1 46 54 83 44
Dr Florent de Vathaire
florent.devathaire@gustaveroussy.fr
+33 1 42 11 54 57

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.

Database : portal towards infrastructures

AIR²D²

Access to Infrastructures for Radiation protection Research

Documented Database

Rechercher dans ce site

HOME OWNER

Exposure platforms

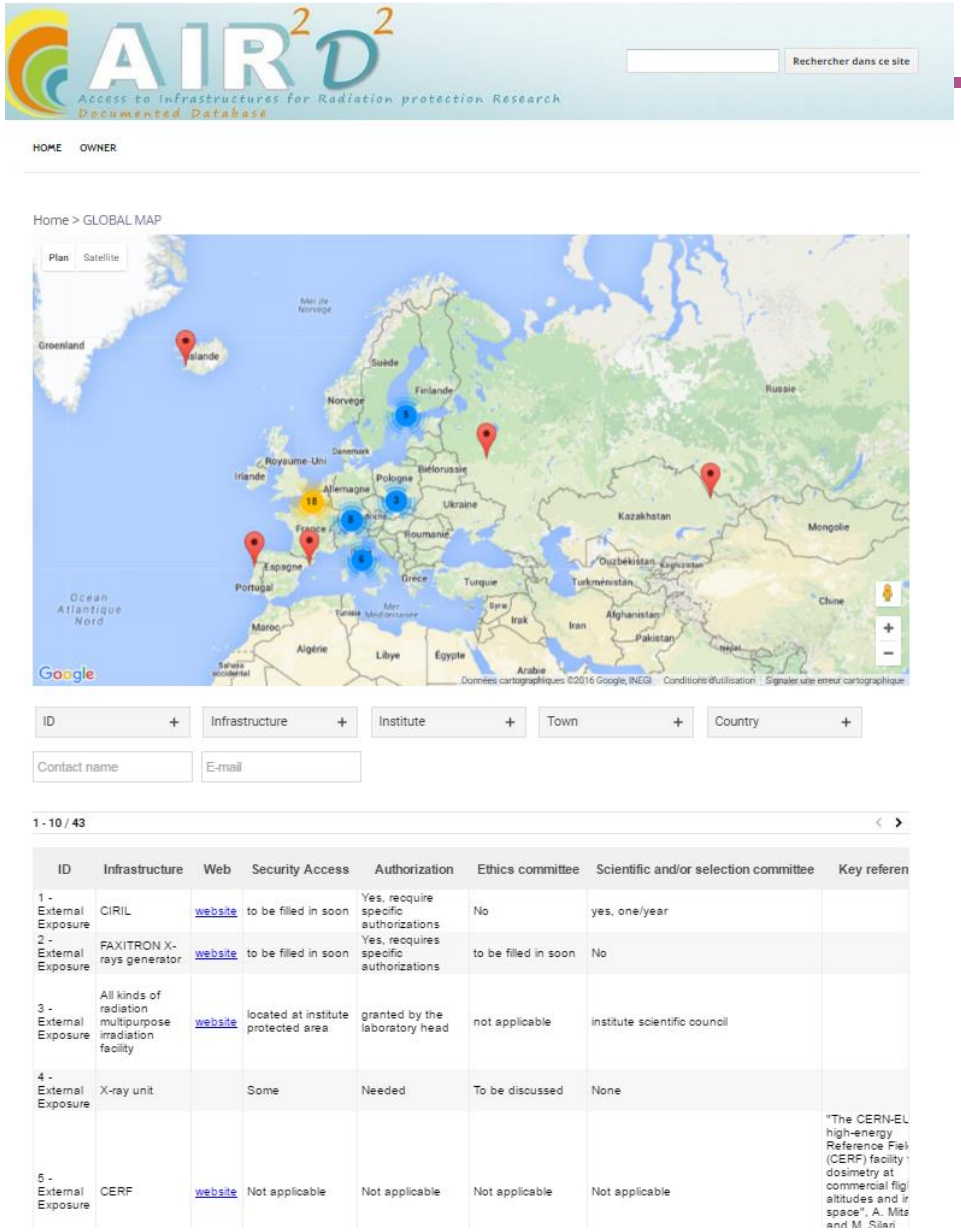
Databases, Sample banks, Cohorts

Analytical platforms, Models, Tools

Global map

Se connecter | Activités récentes sur le site | Signaler un abus | Imprimer la page | Avec la technologie de Google Sites

Database : portal towards infrastructures

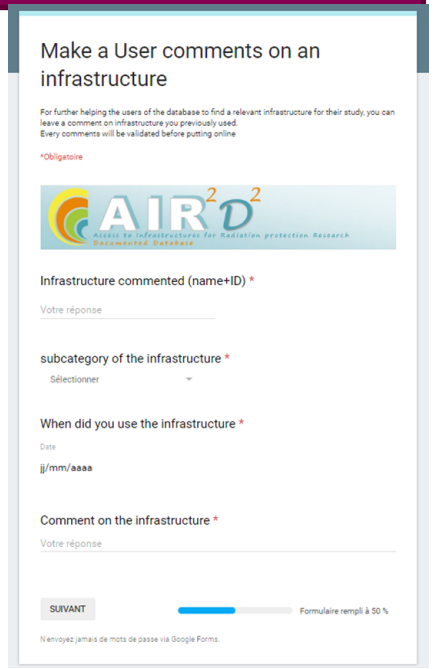


ID	Infrastructure	Web	Security Access	Authorization	Ethics committee	Scientific and/or selection committee	Key referen
1 - External Exposure	CIRIL	website	to be filled in soon	Yes, recquire specific authorizations	No	yes, one/year	
2 - External Exposure	FAXITRON X-rays generator	website	to be filled in soon	Yes, recquires specific authorizations	to be filled in soon	No	
3 - External Exposure	All kinds of radiation multipurpose irradiation facility	website	located at institute protected area	granted by the laboratory head	not applicable	institute scientific council	
4 - External Exposure	X-ray unit		Some	Needed	To be discussed	None	
5 - External Exposure	CERF	website	Not applicable	Not applicable	Not applicable	Not applicable	"The CERN-EU high-energy Reference Fiel (CERF) facility dosimetry at commercial flig altitudes and ir space", A. Mitaı and M. Silari

All the infrastructures on 1 map

Search an infrastructure
Infrastructures of the subcategory
all the criteria : commons + specifics

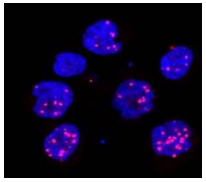
List of all the infrastructures (common criteria)



ANALYTICAL PLATFORMS
BIOMARKERS : INTERCOMPARISON

RENEB
Realising the European Network of Biodosimetry

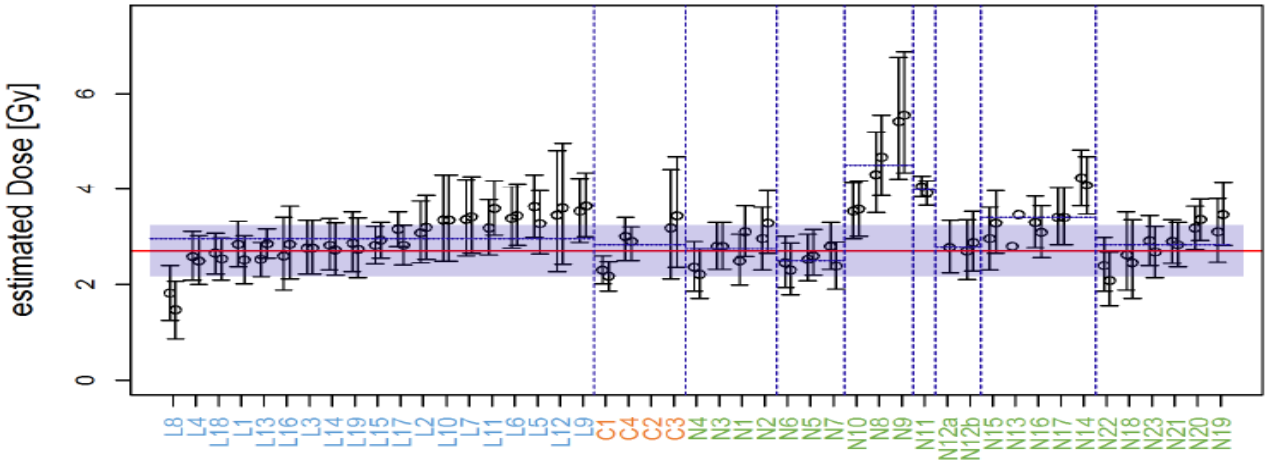
- Gamma H2AX Foci
- Gene expression assay
- Dicentric Assay

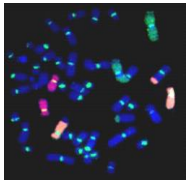


IJRB2017

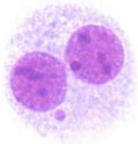
Next ?

Intercomparison biological effect low dose/low dose rate exposure platforms

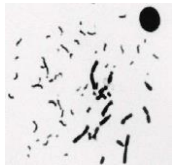




- Fluorescence in situ hybridisation (FISH-Assay)
- Micronucleus assay



- Premature Chromosome Condensation (PCC)



ESA ANNOUNCEMENT

Investigations into Biological Effects of Radiation Using the GSI Accelerator Facility

Cosmic radiation is considered the main health hazard for human exploration and colonization of the solar system: crew members may be exposed to different doses and qualities of radiation, threatening life quality and individual survivability, thereby disrupting mission success. To address these issues, ESA announces an opportunity to propose investigations into biological effects of space radiation using the accelerator facility of the GSI. Experiments should contribute to improved risk assessments or study countermeasures to allow safe and stable human space exploration with acceptable risk from exposure to space radiation.

- Announcement of Opportunity (PDF)
- Letter of Intent template (doc)
- Proposal template (doc)
- Letter of Intent due: **15 September 2017**
- Proposal workshop at GSI (Darmstadt, Germany): **26 September 2017**
- Proposals due: **27 October 2017**

Thanks for your attention

Commissariat à l'énergie atomique et aux énergies alternatives
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