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INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

Faire avancer la sûreté nucléaire

EUROPEAN JOINT PROGRAMME
FOR THE INTEGRATION OF
RADIATION PROTECTION RESEARCH
CONCERT

27th of January, 2016 - Information Day on the 1st OPEN RTD CALL of the 'CONCERT-European Joint Programme for the Integration of Radiation Protection Research' under Horizon 2020

Olivier LAURENT, PhD

IRSN Laboratory of Epidemiology

Topic 1: "Improvement of health risk assessment associated with low dose/dose rate radiation"

Research interests :

low dose/dose rate exposure

internal contamination

Studies on effects of internal contamination at IRSN laboratory of epidemiology

- French cohort of uranium miners – Estelle Rage/Sophie Ancelet

- French cohort of nuclear fuel cycle workers – Eric Samson/Olivier Laurent

- CURE project – Dominique Laurier and CURE consortium

Key words:

- Low dose/dose rate effects
- Internal contamination
- Health risk assessment
- Shape of the dose-response relationships
- Cancer and non-cancer effects

French uranium miners cohort

Aims

► to characterise dose-risk relationships for internal contamination
► cancer-and non-cancer effects

Study design:

- Retrospective cohort of 5,086 uranium miners (Rage et al, IAOEH 2015)
- Follow-up 1946-2012
- Organ doses from radon, uranium and gamma rays estimated
- Smoking, BMI, blood pressure, cholesterol data in nested case-control studies
- Methodological developments (modelling of uncertainties, Bayesian modelling)

Recent results:

- Modelling of measurement error in dose-reponse analyses (Allodji et al, 2012)
- Direct assessment of radiation quality effect of α particles (Rage et al, 2012)
- Case-control study of cardiovascular diseases (Drubay et al, 2015)

Perspectives:

- Bayesian modelling of dose-response relationships (Sabine Hoffman, PhD student)

French nuclear fuel cycle workers: the TRACY cohort

Aims

- ► to characterise dose-risk relationships for internal contamination
- ► Focus on cancer-and non-cancer effects

Study design:

retrospective cohort 12,700 fuel cycle workers (Samson et al, BMJ open 2016)

- Follow-up 1968-2012
- Smoking, BMI, blood pressure, cholesterol: repeated data computerized for 4,500 workers
- Reconstruction of internal doses for 4500 workers (in collaboration with IRSN/SDI/LEDI)
- Exposure parameters and other occupational exposures: Job Exposure Matrices

Recent results:

- Exposure/risk relationships based on Job Exposure Matrices (Canu et al 2010, 2011,
- 2012, Zhivin et al 2015)
- Nested case-control study of cardiovascular diseases (S Zhivin, PhD student)

Perspectives:

- Internal dose /risk analyses (Ségolène Bouet, PhD student)
- Analysis of association between internal dose and blood pressure

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CURE «Concerted Uranium Research in Europe»

Aims

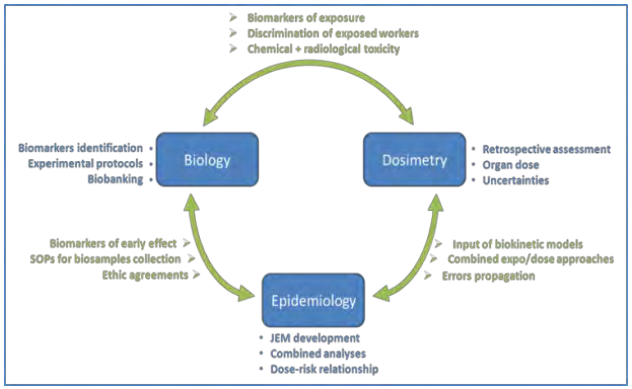
To elaborate a multidisciplinary research project integrating **epidemiology, biology and dosimetry** to improve the assessment of **risks (cancer and non-cancer)** associated with **occupational uranium exposure**

- **Pooled analyses** of **epidemiological** cohorts (miners/workers)
- **Molecular epidemiology** approach

Concerted Uranium Research

- **Concerted Action** supported by **DoReMi**
- **9 European partners**
- July 2013 → Dec 2014
- Coordination : IRSN

DoReMi



Results:

A **protocol** has been **produced** (DoReMi 2015, Laurent et al., submittted; Gueguen et al, in preparation)

Perspectives:

Search for funding to implement the developped research project

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Eric BLANCHARDON

François REBIERE

Radiochemistry laboratory

Laboratory of internal dose assessment

Bioassays laboratory

Internal dosimetry department (research team)

Internal dosimetry

environmental measurement c

i = c x b x t

i = m / M

intake

biokinetic model M

distribution in tissues

emission of radiation

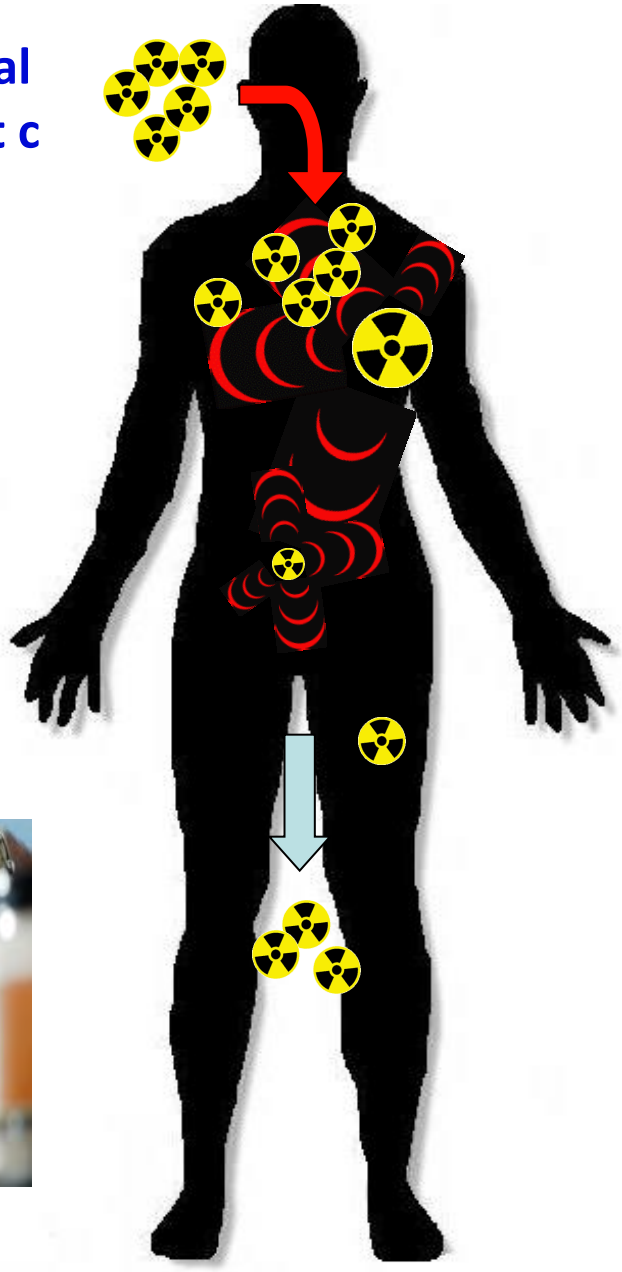
elimination

dosimetric model e

dose

d = i x e

in vivo / in vitro measurement m



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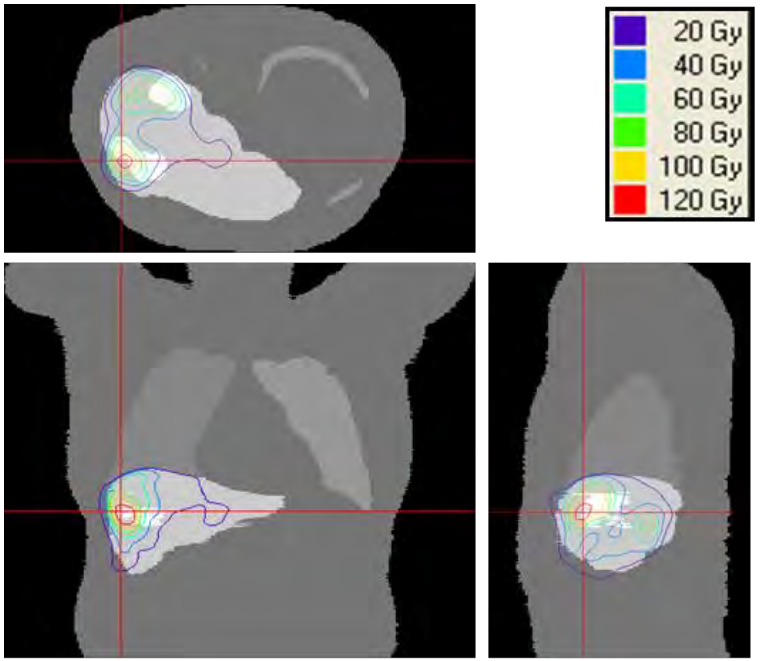
Internal dosimetry main research activities

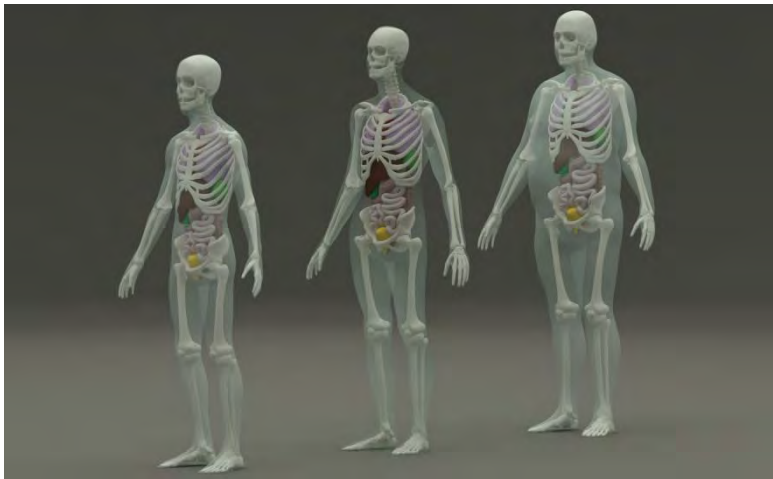
Patient dosimetry in nuclear medicine

- Dosimetry at cellular and organ level
- Development of computer codes (OEDIPE)
- Individual patient images and data from French hospitals
- Application to new targeted radiotherapy protocols



In vivo measurement calibration

- Development of voxel and NURBS phantoms
- Physical organ phantoms with 3D printers
- Application to thyroid monitoring in nuclear emergency (CAThyMARA project within OPERRA)
- Application to staff monitoring in nuclear medicine



Internal dosimetry main research activities

Biokinetic models

- Update of existing models (ICRP-IDC task group)
- Development of computer codes (OPSCI)
- Assessment of uncertainty on dose
- Application to epidemiological studies (Alpha-Risk project in EC FP6, CURE in DoReMi)

Concerted Uranium Research

In vitro measurement of radionuclides

- Localization (SIMS) and speciation of radionuclides in cells and tissues
- Improvement of techniques for actinides measurement
- Application to emergency preparedness (Priodac project, coupling of ICP-MS to calix[6]arene columns for fast and sensitive analysis of U, Pu, Am)

Internal dosimetry department (research team)

Michèle Agarande (head)
Valérie Renaud-Sallis (deputy)

Radiochemistry laboratory

François Rebière (head)
Céline Bouvier
Géraldine Landon
Alexandre Legrand
Annabelle Manoury
Guillaume Phan
David Suhard
Christine Tessier

Laboratory of internal dose assessment

Didier Franck (head)
Nadia Benabdallah
Eric Blanchardon
David Broggio
Cécile Challeton-de Vathaire
Estelle Davesne
Aurélie Desbrée
Leila Gharsalli
Nora Hocine
Ana Taborda
+ 6 non research staff (in vivo measurement)

Bioassays laboratory

Christine Bartizel (head) – 14 staff members, no research activity

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Laboratoire d'ECOtoxicologie des radionucléides

Christelle Adam-Guillermin

Head of laboratory

Research interests : environmental radiological protection

- Predictive ecotoxicology
  - Role of genetic and epigenetic factors on transgenerational effects
  - Drivers of radiosensitivity (DNA damage, protein carbonylation…)
  - Consequences of these molecular changes on survival, behaviour, reproduction, development, longevity
- Biomarkers as biomonitoring tools (Chernobyl, Fukushima)

- Modelling
  - Energy resources management and fitness of organisms (Dynamic Energetic Budget)
  - Prediction of biological effects on population dynamics
  - Long term transgenerational effects (genetic adaptation)

Research interests : human radiological protection

- Predictive ecotoxicology
  - Role of genetic and epigenetic factors on transgenerational cancer effects
  - Drivers of radiosensitivity (DNA damage, protein carbonylation…)
  - Consequences of these molecular changes on survival, reproduction, development, longevity
- Biomarkers as biomonitoring tools (Chernobyl, Fukushima)

- Modelling
  - Energy resources management and fitness of organisms (Dynamic Energetic Budget)
  - Prediction of biological effects on population dynamics
  - Long term transgenerational effects (genetic adaptation)

Research interests : biological models

✓ Biological models widely used for cellular and molecular studies ; sequenced genome

In vivo

Zebrafish

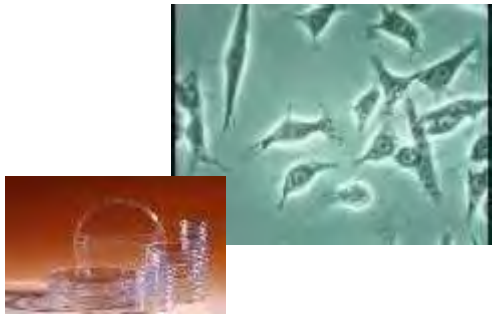
- ✓ Maximal body size < 4.5 cm
- ✓ Generation time < 3 month
- ✓ Radiosensitive

Nematods

- ✓ Maximal body size < 1.5 mm
- ✓ Generation time < 3 days
- ✓ Rather radioresistant

Daphnids

- ✓ Maximal body size < 2 mm
- ✓ Generation time < 21 days
- ✓ Radiosensitive
- ✓ Clonal organism (parthenogenetic reproduction)



In vitro

- ✓ ZF4 zebrafish fibroblastes
- ✓ RTG trout gonad cells
- ✓ Primary cell cultures (hepatocytes and gonads)

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Karine TACK, PhD

Radiotoxicology Laboratory

Study on effects of ionizing radiations at low doses on health after :

→ internal contamination (U, Cs, Sr, ^{3}H, …) for ingestion and inhalation exposure pathways

→ external irradiation

Different organs/systems : Central nervous system (CNS), cardiovascular, kidney, hematopoietic, reproduction, metabolic (D Vitamin, xenobiotics, cholesterol, …) systems

On CNS : neurogenese, neuroinflammation, synaptic transmission, transport/transfer mechanisms (BBB, olfactory nerve), behavior analysis

On cardiovascular system : atherosclerose, inflammation, adaptation mechanism

In vivo studies on Uranium :

- transgenerational study (3 generations)
  - CNS, reproduction, metabolisms, metabolomic and epigenetic analyses
- *in utero* and post-natal study (neurogenesis)
- Nose-only system (micro and nanoparticles) :
  - olfactif nerve transfer / brain effect

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Sophie JACOB, PhD

Radiation epidemiologist

Research interests

Laboratory of Epidemiology - Medical exposure

Side effects of radiotherapy

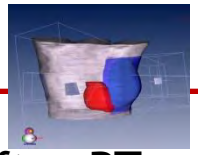
molecular epidemiology

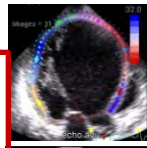
- Heart : BACCARAT study – Sophie Jacob
- Brain: EPIBRAINRAD – Marie-Odile Bernier

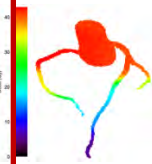
Early detection and prediction of cardiotoxicity after radiation therapy for breast cancer: the BACCARAT study

sophie.jacob@irsn.fr

Much before clinical onset of cardiac dysfunction arising 5-10 years after breast RT: First cardiac changes ?







Aims:

► to evaluate the occurrence of subclinical cardiac changes occurring after RT based on functional and anatomical cardiac imaging,

► to define the potential role of circulating biomarkers in the assessment of RT-related cardiotoxicity (work performed with biologists R Tamarat, F Millat IRSN)

► to evaluate heart absorbed doses : whole heart and substructures (work performed with dosimetrists D Broggio and S Derreumaux IRSN)

► dose-response relationships and normal tissue complication probability (NTCP)

➢ **Study design** : Prospective monocentric cohort of 120 breast cancer patients treated with 3D-CRT, without chemotherapy, aged 50-70 years, followed for 2 years (biomarkers, cardiac imaging)

Results: The study is currently recruiting participants. Inclusions started in October 2015 (20 patients included). End of inclusion in 2017. End of study 2019

Conclusion: improving knowledge on cardiotoxicity and anticipating the cardiac risk after breast RT

Study of Neurological Complication After Radiotherapy for High Grade Glioblastoma EPIBRAINRAD

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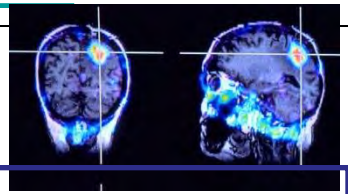

To gain further insight in the radiation-induced leukoencephalopathy

Aims

► to study the onset and evolution of leukoencephalopathy using specific cognitive tests, Magnetic Resonance Imagery (MRI) scans of the brain

► to study predictive bio-markers of cognitive impairments (work performed with biologists R Tamarat, F Millat, P Lestavel IRSN)

► To study the relation between the risk of leukoencephalopathy and the received dose to the brain

➢ **Study design** : a 3-year prospective cohort of 200 adult patients having undergone cerebral radiotherapy for glioma (stage 3-4), who will be followed every 2-3 months for a period of 3 years after enrolment (biomarkers, neuro-psychological tests, MRI scans).

Results: The study is currently recruiting participants. Inclusions started in May 2015 (35 patients included). End of inclusion in 2018

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Exposure to IR during childhood

Epidemiology

- COCCINELLE study - Hélène Baysson
- Cohorte Enfant-Scanner - Marie-Odile Bernier

The « *cohorte Enfant Scanner* »

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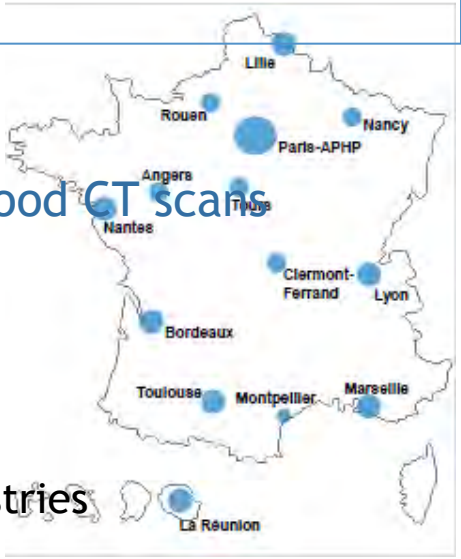
Main objectives:

Assessment of exposure to CT scans in paediatrics

Analysis of cancer risk related to cumulative doses from childhood CT scans



Study population:

- Children born ≥1995 without cancer diagnosis at the 1st CT scan exposed in 2000-2011 to a 1st CT scan < the age of 10 years
- 23 radiology departments of major university hospitals in France
- Follow-up of cancer incidence and mortality through national registries

► 67 274 children included (≥1 year of follow-up)

Median duration of follow-up = 4 years

► Exposures

Young ages at the first examination

Low cumulative doses =7 mGy

► Incident cases (>1 year after the 1st CT scan)

106 incident cases of cancer

27 tumors of the CNS, 25 cases of leukemia, 21 of lymphoma

Included in EPI-CT European project

Soon possible to obtain cardiovascular events based on database from French health Insurance

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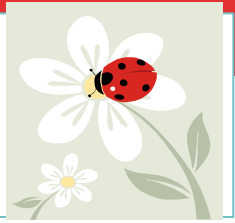
The “COCCINELLE*” study

helene.baysson@irsn.fr



*Ladybird

A nationwide cohort (retrospective, prospective) of children who underwent a Cardiac Catheterization Procedure before the age of 10, in 2000–2013 in France *[Baysson et al. BMC Pub Health 2013]*

- **Evaluation of the doses delivered during CCPs in paediatrics in France**
- **Assessment of the subsequent risk of cancer**
  - Recruitment from all departments of paediatric cardiology (15 hospitals)
  - Expected population size: **8 000 children**
  - Individual dosimetric reconstruction
  - Mortality and cancer incidence retrieved through the national registries

Preliminary results for the 2 largest centres (Necker and Marie-Lannelongue Hospitals)

- 6 754 CCPs before the age of 10 in 4 865 children (77% of children with 1 CCP)
- **Mean effective dose (mSv)** (PCXMC 2.0)
  Diagnostic CCP: 4.8 (min-max = 0.3-23)
  Therapeutic CCP: 7.3 (min-max = 0.1-48)

✓ First linkage with cancer registries scheduled in 2016
✓ Evaluation of the potential risk of cancer induced by CCP using a quantitative risk assessment approach

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Laurence Roy, PhD

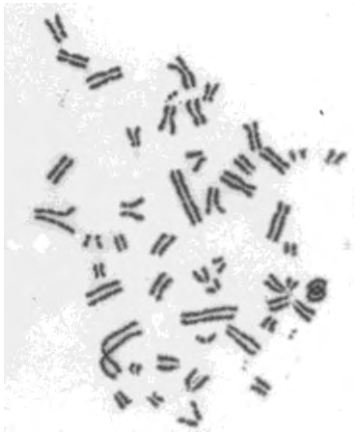
Radiation biology and epidemiology department

Research interests

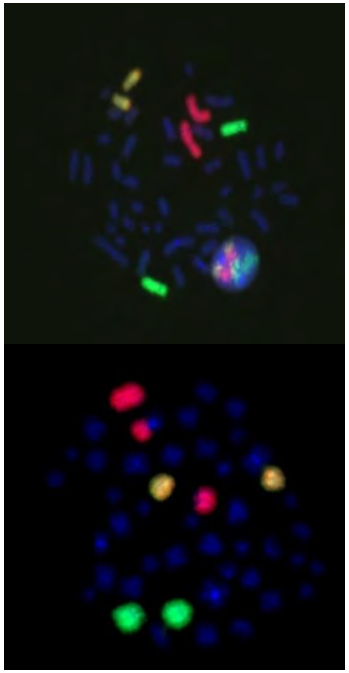
Biological dosimetry – Biomarkers

Infrastructures

Chromosomal aberration analysis: human and mouse



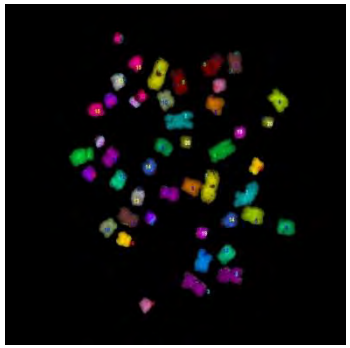
Dicentrics
PCC
3P-FISH
M-FISH

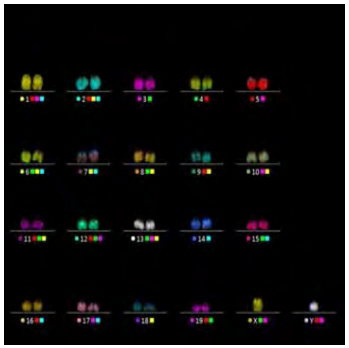


cofrac
ESSAIS

ISO 17025

RENEB
Realising the European Network of Biodosimetry





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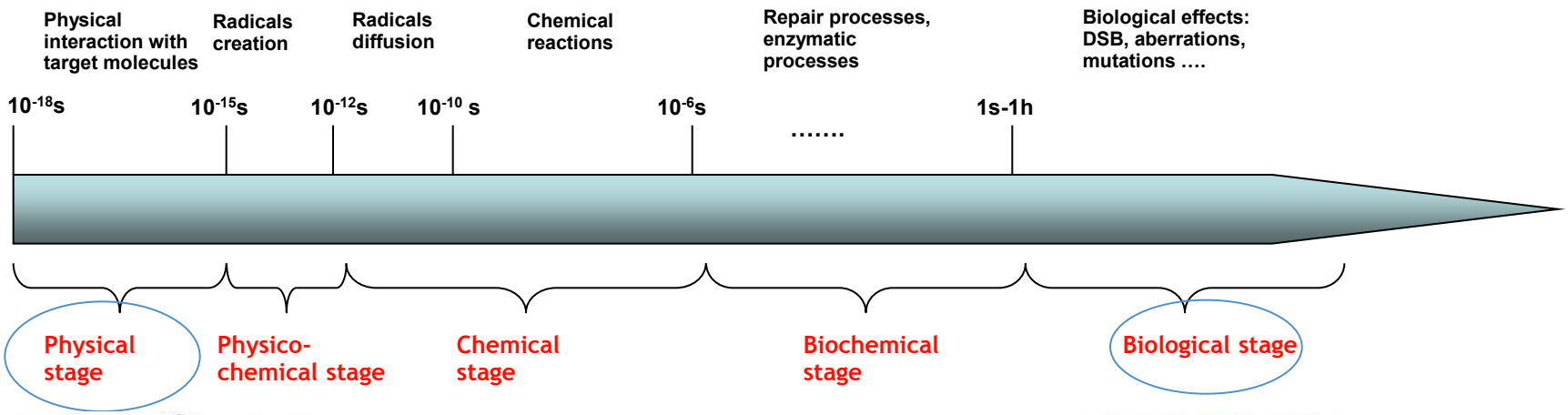
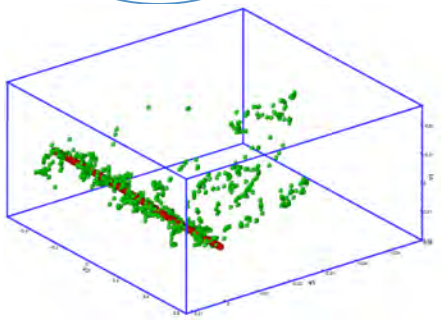
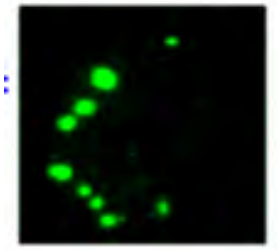
Nanodosimetry : Track structure simulations using Monte Carlo





Simulation

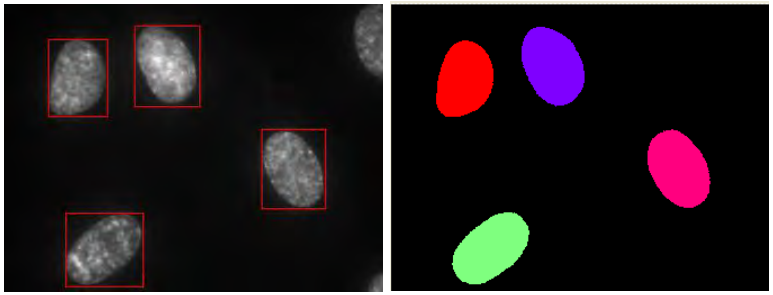


Dedicated biological data are measured using **microbeam** facilities (PTB, Surrey university)

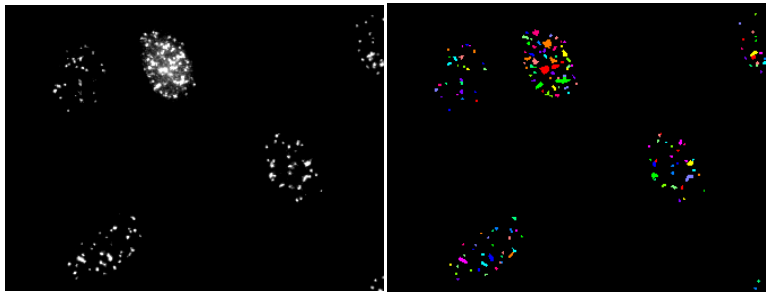
Observations

Méthodologie

- Logiciel d'analyse d'image basé sur LabVIEW



Détection des Noyaux



Détection des Foci

Plusieurs milliers de noyaux analysés par condition

Plusieurs dizaines de milliers de foci analysés par condition

IRSN Infrastrucutures

Internal contamination Platform: Parisii 5 000 animals – rats and mice

- Animal experiments : contamination via ingestion and µ and nP inhalation (glovebox)

- Radionuclides : U, Sr, Cs, 3H, 14C Co, Pb, I, Fe, Na, Ca,…

- Different labs covering:
  - physical measurements (spectrometry α, β, γ),
  - radiochemistry,
  - electron microscopy lab
  - electrophysiology laboratory,
  - behavior laboratory: (Open field, Water Morris maze, Y maze, Porsolt-Test, elevated plus maze, telemetry method)
  - biological analysis laboratories : histology, 2 P2 laboratories for cultured cells contaminated, molecular biology, biochemistry physiology

Infrastructures

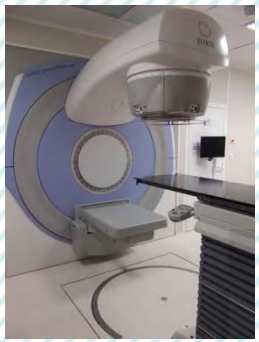
❑ Gamma irradiator MICADO (Cs-137)

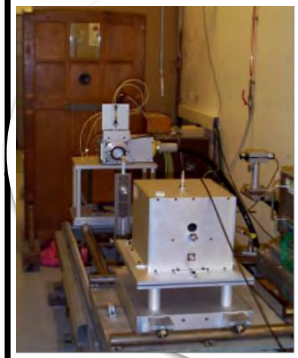
❑ Contamination area

- Depleted and enriched uranium
- Gamma, beta (e.g. glovebox for tritium), alpha emitters (e.g. Am 241)

IRSN: photons installations

X-rays





X-Ray and
Co60/Cs137

AMANDE

10 Gy
1 Gy
100 mSv
10 mSv
1 mSv

High doses
Low doses

10 keV
100 keV
1 MeV
20 MeV
Energy

Radiation biology

Radiation biology
Médicale applicati

Métrologie
Radiation
protection

IRSN

A fleet of mobile units for Accident Monitoring of Internal Contamination

Sending the most appropriate mobile unit to the field (10 hours)

- 4 fast truck labs with whole body and thyroid contamination counters (400 p/d, 10 min counting time, NaI(Tl) detectors)
- 4 shelters with quick whole body and thyroid contamination counters (1000 p/d, 10 min counting time, NaI(Tl) detectors)
- 2 heavy trucks for expertise of internal contamination (80 p/d -GeHP detectors)

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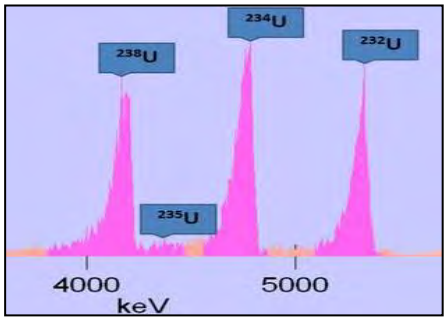
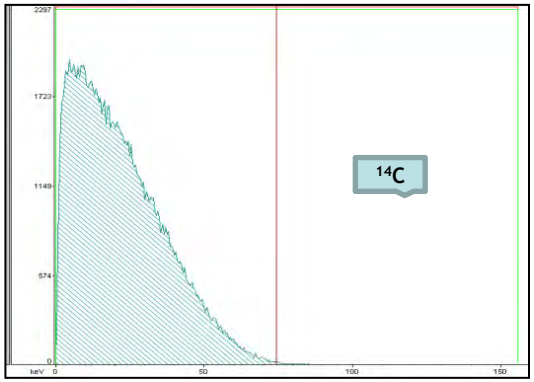
Biossays Laboratory

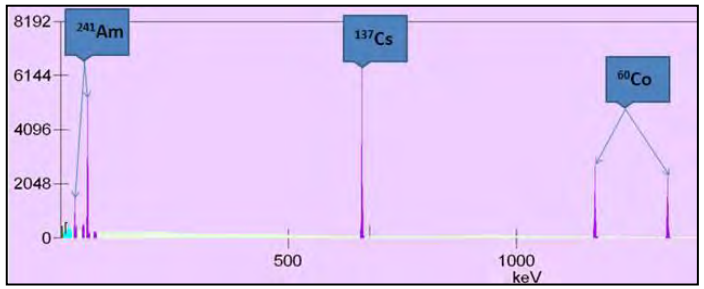
Alpha spectrometry



Liquid scintillation



Gamma spectrometry



Bq/L

α emitters

$^{238\text{-}239}Pu$, $^{241\text{-}243}Am$, $^{228\text{-}230\text{-}232}Th$, ^{226}Ra, $^{234\text{-}235\text{-}238}U$

β emitters

^{3}H, ^{14}C, $^{32\text{-}33}P$, ^{35}S, ^{36}Cl, ^{45}Ca, ^{55}Fe, ^{63}Ni, $^{89\text{-}90}Sr$, ^{90}Y, ^{169}Er

directs γ spectrometry

$^{123\text{-}125\text{-}131}I$, ^{99m}Tc, ^{67}Ga, ^{201}Tl, ^{111}In, ^{51}Cr, $^{58\text{-}60}Co$, ^{137}Cs

IRSN

Competencies and research interests

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Information Day: CONCERT – European Joint Programme for the Integration of Radiation Protection Research

Munich, 27 th of January, 2016

RĪGAS STRADIŅA UNIVERSITĀTE
VITA BREVIS ARS LONGA

Competences (1)

- Extensive epidemiological and clinical research on Chernobyl nuclear power plant clean-up workers' health conditions has been done in Latvia during more than 20 last years.
- The comprehensive data on health observations in Chernobyl NPP clean-up workers from Latvia (approximately 6000 people) were collected since the disaster time (1986) till now in the State Register of Persons Exposed to Ionizing Radiation in Chernobyl Accident.

Competences (1)

- Previous studies included the analysis of late aftereffects of prolonged exposure to low doses of ionizing radiation after nuclear power plant disaster:
  - immunological evaluation of changes in the immune system (including immunosenscence),
  - biochemical studies of oxidative stress and other molecular disturbances followed the exposure,
  - retrospective biodosimetry (from teeth enamel),
  - morphological features of thyroid gland diseases,
  - electroneurological and psychological evaluation,
  - genetic studies (telomere length analysis),
  - cause specific morbidity and mortality of CNPP clean-up workers from Latvia compared with general Latvian population.

Research interests in the future

- Collaboration study in field of molecular epidemiologic evaluation to compare populations from different countries previously exposed to ionizing radiation (e.g., Chernobyl accident clean-up workers from Latvia, Lithuania and Estonia, A-bomb survivors in Japan).
- The retrospective biodosimetry based on the analysis of immune and genetic parameters supported by epidemiological data from previous health observations and data bases.
- Epidemiological data on oncological morbidity and cause specific mortality in whole exposed population.

Thank You for Your Attention and Welcome to Riga (Latvia)!

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