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C2-05: Creation of national standards for some emerging pharmaceutical radionuclides to ensure the radioprotection of patients and medical staffs

Project Leaders:

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Definition of the project

- **Creation of national standards through an integrated metrological chain for new radionuclides** (^{186}Re, ^{82}Sr-^{82}Rb, ^{177}Lu, ^{90}Y) used in nuclear medicine, to ensure the radioprotection of patients and medical staffs.

- **<u>State of the art :</u>**

Nuclear medicine involves the injection of radiopharmaceuticals that target specific diseased tissues and physiological processes.

It permits :

- the extent of the disease or non-normal functioning to be visualized with modern nuclear medicine imaging techniques, like scintigraphy or positron emission tomography (PET)

- the delivery of therapeutic radiation doses to those tissues for treatment while minimizing damage to healthy tissues.

Need of safety and effectiveness of radiopharmaceuticals :

- the ability of the radiopharmacy to deliver the prescribed amount of radioactivity.
- needs of an accurate measurement of the amount of radioactivity contained in the drug prior to its administration.

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Definition of the project

- For diagnostic purposes :

- too much radioactivity : excess of dose delivered to the patient, cause of further damage
- an insufficient amount : poor imaging, and either a possible diagnostic error or the requirement to repeat the protocol with the correct dose.

- For therapeutic purposes :

- the therapeutic effect and possible damage to healthy tissues is directly related to the administrated activity.
- Importance of the accurate knowledge of the administrated activity for the accurate determination of the therapeutic window of this new radiopharmaceutical.

→ Fast and easy access to accurate calibration factors is therefore important during clinical trials

The **calibration factors are specific to each radionuclide** (type, energy, and intensities of emitted particles per disintegration), in a given container

→ each time a new radionuclide has to be used, the instrument has to be calibrated for it.

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Definition of the project

- From those considerations, R&D effort in metrology laboratories :

- to create national activity standards for new radiopharmaceuticals which can be disseminated to practitioners in the medical field through secondary standards;

- to establish an international metrological infrastructure bringing significant input to the key comparison data base (KCDB) at the *Bureau International des Poids et Mesures* (BIPM);

- To determine nuclear decay data such as absolute emission intensities of x- rays, annihilation and gamma photons, conversion and Auger electrons and the half-life with high accuracy.

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IFIN-HH/LNHB Staffs

- IFIN-HH : Members:
  - A. Luca: X- and gamma-ray spectrometry, nuclear data
  - M. Sahagia: head of the Radionuclide Metrology Laboratory, coincidence counting
  - C. Ivan: liquid scintillation
  - A. Antohe (young researcher): preparation of radioactive standards, liquid scintillation, IC
  - B. Neacsu (young researcher): gamma-ray spectrometry
- LNHB : Members:
  - T. Branger : head of the laboratory of metrology of radioactivity
  - M.-M. Bé : nuclear data
  - M.-C. Lépy : gamma-ray spectrometry
  - P. Cassette : liquid scintillation
  - C. Bobin : coincidence counting
  - V. Lourenço (young researcher) : preparation of radioactive standards
  - C. Thiam (young researcher) : well-type + coincidence counting
  - M. Rodrigues (young researcher) : calorimetry

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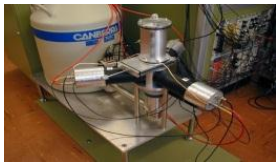
Tasks of the C2-05 project

- Common measurements to obtain primary standards of these radionuclides, by using absolute standardization methods:

  - the LSC-TDCR liquid-scintillation counting (LNHB/IFIN-HH),

  - the 4πβ-γ coincidence (LNHB/IFIN-HH),



  - the calorimetry technique (LNHB).

- Delivery of an ampoule containing the same nuclide to the BIPM for participation to the International System of References (SIR) in order to create or improve the international Key Comparison Reference Value (KCRV) (LNHB/IFIN-HH).

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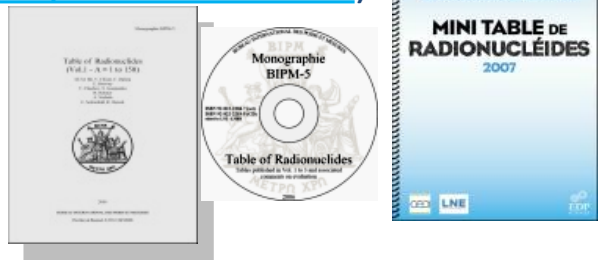
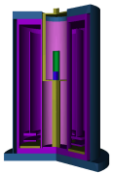
Tasks of the C2-05 project

- Theoretical and experimental studies to improve or determine the nuclear decay scheme data of these nuclides, important for the dose calculations. According to the results, a new decay scheme might be proposed in the framework of the international co-operation “Decay Data Evaluation Project” (DDEP) (LNHB/IFIN-HH) The NUCLEIDE database (http://www.nucleide.org/DDEP_WG/DDEPdata.htm) will be updated (LNHB).



- Creation of secondary standards through the Ionization Chambers (IC) or gamma spectrometry (GS) instruments which can be easily transferred to the nuclear medicine services in hospitals (LNHB/IFIN-HH).


Ionization Chambers


Gamma Spectrometry

- Dissemination of the results obtained, by common participation in international conferences / workshops and publishing articles in international ISI-quoted journals (LNHB/IFIN-HH)

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Methodology

- Both laboratories have experienced staff with many publications in the field, and some young researchers; mostly, the existing measurement equipments will be used.

- The radionuclides will be bought from commercial producers, the radioactive solutions/source preparations will be done in the radiochemistry rooms of the labs.

- Because the radionuclides proposed for study disintegrate by different ways, the proposal includes several absolute activity standardization methods :

- the **4πβ-γ coincidence method** (variant of detection efficiency extrapolation),
- **liquid-scintillation counting measurement** including the triple-to-double coincidence ratio method (TDCR), combined with the **detection efficiency computation for electron and photon radiations based on ETNA, the Monte-Carlo code PENELOPE and other models**,
- and the **calorimetry method**.

The absolutely standardized solutions will be used as follows:

- Organization of comparisons (bilateral, BIPM-Systeme International de Reference (SIR))

- Solid sources preparation for X-ray and gamma-ray spectrometry mesurements: determination of photon emission intensities and radionuclidic purity.

- Comparison of the measured and published emissions values; Data compilation and evaluation: recommended values will be proposed for the nuclear databases.

- Preparation of vials filled with standard radioactive solutions for the calibration of secondary measuring systems (pressurized 4π ionization chambers, gamma spectrometers), used for the transfer of the new standards to nuclear medicine users.

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Results

- **Purchase, assembling, testing and calibrating of a new X-ray spectrometric system at IFIN-HH** . IFIN-HH will purchase a new system to analyze the X-ray spectra obtained with the X-ray Si(Li) detector, in order to determine the emission intensities of X-rays and low energy gamma-rays (below 50 keV): deliverable date 30/11/2012

- Participation to DDEP-2012 Workshop (LNE, Paris: 08-10/10/2012): Organised by LNHB

- Nov. 2013 : Study of the radionuclides ^{186}Re and ^{177}Lu: purchase of radioactive solutions, documentation, common activity measurements and comparisons, nuclear data measurements and evaluation, reporting and writing articles for journal publishing (LNHB/IFIN-HH).

- Nov. 2014 : Common measurements of ^{82}Sr-^{82}Rb and ^{90}Y at CEA/LNHB (IFIN-HH participation). Organization of an international workshop by IFIN-HH.

- Sr-82 : collaboration between CEA and ARRONAX (Nantes, France), producer of ^{82}Sr-^{82}Rb, ^{211}At, etc.

- Feb. 2015: Writing a common paper for publication. The final report of the project. (LNHB/IFIN-HH).

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Results

Crt. No.	Stage	Activities to be performed	Participant	Working period
1	X-ray spectrometric system at IFIN-HH	Purchasing, assembling, testing and characterizing (calibrating)	IFIN-HH	2012, Mar.-Nov.
2	Radionuclides study (^{186}Re, ^{177}Lu)	Radioactive solutions, absolute standardizations, comparisons, data evaluation, reports and articles	CEA-LNHB, IFIN-HH	2012, Dec. -2013, Nov.
3	^{82}Sr-^{82}Rb and ^{90}Y measurements. Workshop.	Radioactive solutions, absolute standardizations, comparisons, data evaluation, reports, articles. Organization, results dissemination, report.	CEA-LNHB, IFIN-HH	2013, Dec. -2014, Nov.
4	Final Project Report	Issue, evaluation of the Final Report	CEA-LNHB, IFIN-HH	2014, Dec. - 2015, Feb.

Contribution of the project

- LNHB :

In CEA, the **Laboratoire National Henri Becquerel** (LNHB) is the French national metrology laboratory for ionizing radiation.

- World leader in the elaboration of absolute activity standardization methods, design and assembling of high-precision systems for experimental determination of nuclear data.
- LNHB coordinates the international co-operation Decay Data Evaluation Project (DDEP) and hosts the associated nuclear database (NUCLEIDE).
- LNHB already provides the standardization of various pharmaceutical radionuclides, such as ^{131}I or ^{18}F, to users.

→ The standardization and improvement of decay data for radionuclides emerging in the field of nuclear medicine is one of the ongoing multi-annual R&D projects of LNHB.

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Contribution of the project

- IFIN-HH :

Presently, in Romania the radionuclide ^{131}I is traditionally used for targeted therapy of the thyroid cancer, while the radionuclides ^{99m}Tc and ^{18}F are used for diagnostic procedures.

- The Radionuclide Metrology Laboratory (LMR) assures the whole traceability chain for ^{131}I and ^{99m}Tc. In IFIN-HH, the Radioisotopes and Radiation Metrology Department, in co-operation with the Oncology Institute of Bucharest, is studying the implementation, with better therapeutic performances, of the radiopharmaceuticals based on biomolecules labelled with the radionuclides ^{177}Lu, ^{186}Re, ^{188}Re. LMR is involved in these studies, by elaborating precise standardization methods. LMR participates at high precision activity measurements of different organs, in bio-distribution studies for the new radiopharmaceuticals. Other radionuclides (PET) under study are: ^{68}Ga, ^{18}F, ^{67}Cu, ^{124}I

(project PN-II-ID-PCE-2011-3-0070, Ctr. 23/05.10.2011, Dr. M. Sahagia).

Training for the 2 institutions: reinforcement of the collaboration between the IFIN-HH and CEA/DRT/LIST/LNHB. It will make possible the exchange and training of new young researchers for both laboratories.

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Contribution of the project

- For the European interest:

Implementation of a high performance metrological system with applications to targeted radiotherapy, based on the use of labelled radio-molecules (Radiopharmaceuticals) : priority for the European metrology system, EURAMET, included in the European Metrology Research Programme (EMRP).

Recently, at the EMRP Call 2011 – Health, a project was proposed: Joint Research Project (JRP) MetroMRT (Metrology for molecular radiotherapy). The project approaches the most precise methods to implement the integrated metrological system.

Participation of LNHB and IFIN-HH in the EMRP JRP ENG08 MetroFission: Metrology for new generation power plants (2010-2013) :

- Organisation of a workshop by IFIN-HH in 2013, dedicated to the field of nuclear decay data, with the foreseen participation of experts involved in the JRP ENG08, DDEP → possibility of a fruitful meeting of the French and Romanian specialists involved in the proposed CEA-IFA project.

- Common workshop, to be organized by the end of 2014, at IFIN-HH.

Perspectives of the project

- Traceability links with hospitals for all the radionuclides (^{186}Re, ^{82}Sr-^{82}Rb, ^{177}Lu, ^{90}Y)
- Recently, a new producer (ARRONAX, Nantes (France)) expressed a need for the calibration of their measuring equipments for newly-produced nuclides (*e.g.* ^{82}Sr-^{82}Rb, ^{211}At, etc.) for which there are no available standards.
- New measurement methods for ^{90}Y are worth being studied (EMRP Project : HLT11 MetroMRT (Molecular RadioTherapy)).
- Scientific exchanges following on short term (LNHB/IFIN-HH):
  - IFIN-HH at LNHB : Nov. 2012 or early 2013: visit of the gamma-ray spectrometry, TDCR units
  - LNHB at IFIN-HH : visits for the TDCR method (Dec. 2012 or Jan. 2013).

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THANK YOU FOR YOUR ATTENTION !