NPL

MetroMRT 3rd Workshop:

"Clinical implementation of dosimetry for molecular radiotherapy"

National Physical Laboratory, Teddington, UK
20-21 April 2015

EURAMET

EMRP
European Metrology Research Programme
Programme of EURAMET

The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union

MetroMRT
Metrology for Molecular Radiotherapy

MetroMRT

("Metrology for molecular radiotherapy")

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- Collaborative project part-funded by the EC through the European Metrology Research Programme
- 6 national metrology laboratories
- 8 clinical research centres
- 23 collaborating institutions
- 8 different countries
- It started on 1 June 2012 and will end 31 May 2015
- The overall aim of the project is to develop an "accepted protocol" for calibrating and verifying clinical dosimetry measurements in MRT.

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The programme of the workshop

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1. Present and discuss the results and recommendations of the project
2. Investigate European and international attitudes to the need for dosimetry in MRT
3. Presentations from European centres where MRT dosimetry has been successfully introduced.
4. Investigate the role of dosimetry in multi-centre clinical trials and the role of multi-centre clinical trials in dosimetry
5. General discussion

The issues

The underlying themes:

- Mixing metrology with clinical practice
- "Metrological legitimacy": Traceability
  Standardisation

The "subliminal debate"

No dosimetry *vs* Dosimetry

Bad dosimetry *vs* good dosimetry

Everyone does their best *vs* everyone does the same

This is a *work*shop

There are scheduled discussion sessions where your contribution will be very much appreciated

Please participate and enjoy the workshop!

The MetroMRT project: towards a dosimetry protocol for MRT

Vere Smyth[1], Christophe Bobin[2], Lena Johansson[1], Leila Joulaeizadeh[3], Marco D'Arienzo[4,5], Marco Capogni[4], Hans Rabus[6], Maurice Cox[1], Jaroslav Šolc[7]

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[2]Commissariat a l'Energie Atomique (CEA), France
[3]VSL, Dutch Metrology Institute, Netherlands
[4]National Institute of Ionizing Radiation Metrology, ENEA-INMRI, Italy
[5]Sapienza University of Rome, Italy
[6]Physikalisch-Technische Bundesanstalt (PTB), Germany
[7]Czech Metrology Institute (CMI), Czech Republic

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MRT (molecular radiotherapy)

- Critical radiation doses :
  - To target (is the treatment effective?)
  - To normal tissue (can you give enough activity?)
- Difficult to measure dose so treatment based on “population” prescription of activity from clinical trials
- The standard administered activity (adjusted for patient size) is based on what is “safe” for 95% of treated patients
- *This means that up to 95% of patients are under-dosed and could have received a more effective treatment!*

Same Activity = Same Dose?

- Mean absorbed doses from fixed or weight-based administrations
- I-131 NaI for thyroid ablation: remnant dose
  - 7 – 3,500 Gy (O'Connell et al - *Radiother Oncol 1993*)
  - 1.2 – 540 Gy (Sgouros et al - *J Nucl Med 2004*)
- Y-90 Zevalin for NHL (Wiseman et al - *Cancer 2002*)
  - Red marrow 0.3 – 1.2 Gy
  - Tumour dose 0.6 – 243 Gy
- I-131 mIBG, neuroblastoma (Matthay - *JNM 2002*)
  - Tumour absorbed doses: 3-305 Gy (for 555MBq/kg)
- Y-90 DOTATOC for NETs (Bodei et al - *EJNM 2004)*
  - Kidneys 6 - 46 Gy
  - Marrow 0.2 – 1.9 Gy

First consider the measurement chain used in external beam radiotherapy:

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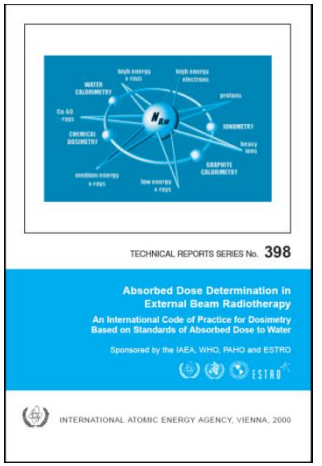

1. Dosemeter calibration against primary standard
2. Dose rate measurement under reference conditions in the user's beam (Gy/MU)
3. Calculation of 3D dose distribution in the patient (per MU) using a TPS that has been commissioned and validated using "best practice medical physics"
4. Dose to the ICRU reference point within 5% of the prescribed dose

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Analysis of the links in the MRT dosimetry chain

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1. Measurement of the administered activity;
2. Definition and delineation of the volumes of interest (target tissue; normal tissue);
3. Quantitative imaging (QI) procedure (tracer activity, full therapy activity, surrogate RP) to determine activity in the volume of interest relative to the administered activity;
4. Determine biokinetics from a time sequence of activity measurements interpolated/extrapolated to give an activity-time curve; then obtain total disintegrations within defined volumes of interest by integrating under the curve;
5. Calculation of absorbed dose within the volume of interest (Gy/MBq).

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MetroMRT workpackage structure

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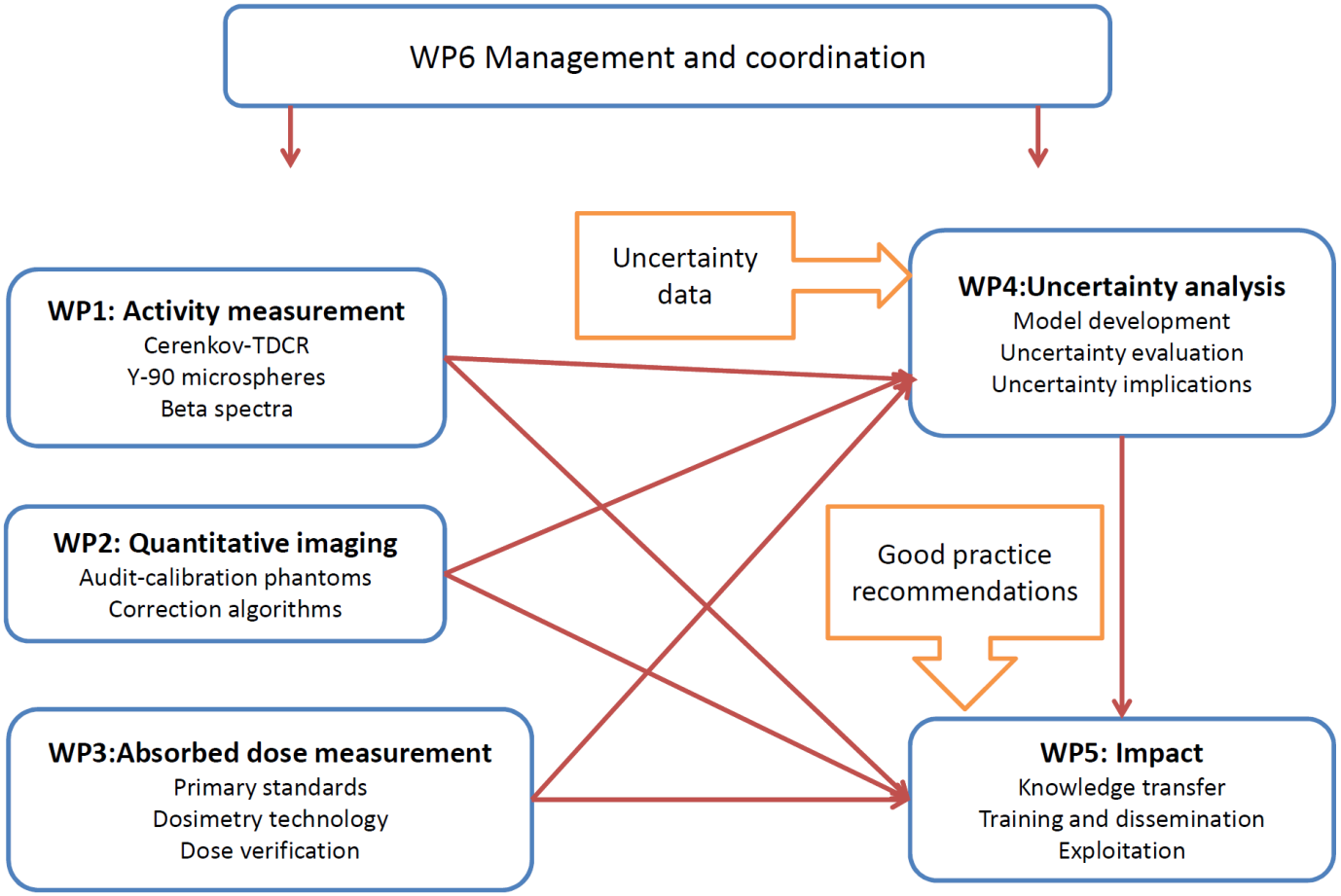

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Workpackage 1:
Activity measurements for molecular radiotherapy

- Task 1.1: Development of the TDCR-Cerenkov technique for use as a primary standard for radiopharmaceuticals (CEA)
- Task 1.2: Development of standards and transfer methods for 90Y microsphere samples (NPL)
- Task 1.3: Determination of beta spectra (CEA)

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Workpackage 2:
Quantitative Imaging for Molecular Radionuclide Therapy

- Task 2.1: SPECT/PET activity quantification and imaging techniques (NPL)
- Task 2.2: Calibration phantom (NPL)
- Task 2.3: Correction factors and algorithms (ENEA)

Workpackage 3:
Measurement of absorbed dose from radionuclides

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- Task 3.1: Development of absorbed dose measurement techniques and procedures for MRT dosimetry based on dosimeter calibrations against the existing absorbed dose primary standards for external beams (VSL)
- Task 3.2: Feasibility study for the development of a primary absorbed dose standard for radionuclides (ENEA)
- Task 3.3: Development of prototype standards based on the feasibility studies from Task 3.2 (ENEA)
- Task 3.4: Assessment and validation of methods for obtaining absorbed dose from cumulative activity (NPL)
- Task 3.5: Feasibility of a dosimeter measuring biological outcomes of radionuclide exposure (PTB)

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Task 3.1: Development of absorbed dose measurement techniques and procedures for MRT dosimetry based on dosimeter calibrations against the existing absorbed dose primary standards for external beams (VSL)

3.1.1: Comparative analysis of previous works on absorbed dose measurements from radionuclides

3.1.2: Decision made as to whether to include any other measurement techniques in Task 3.1.1

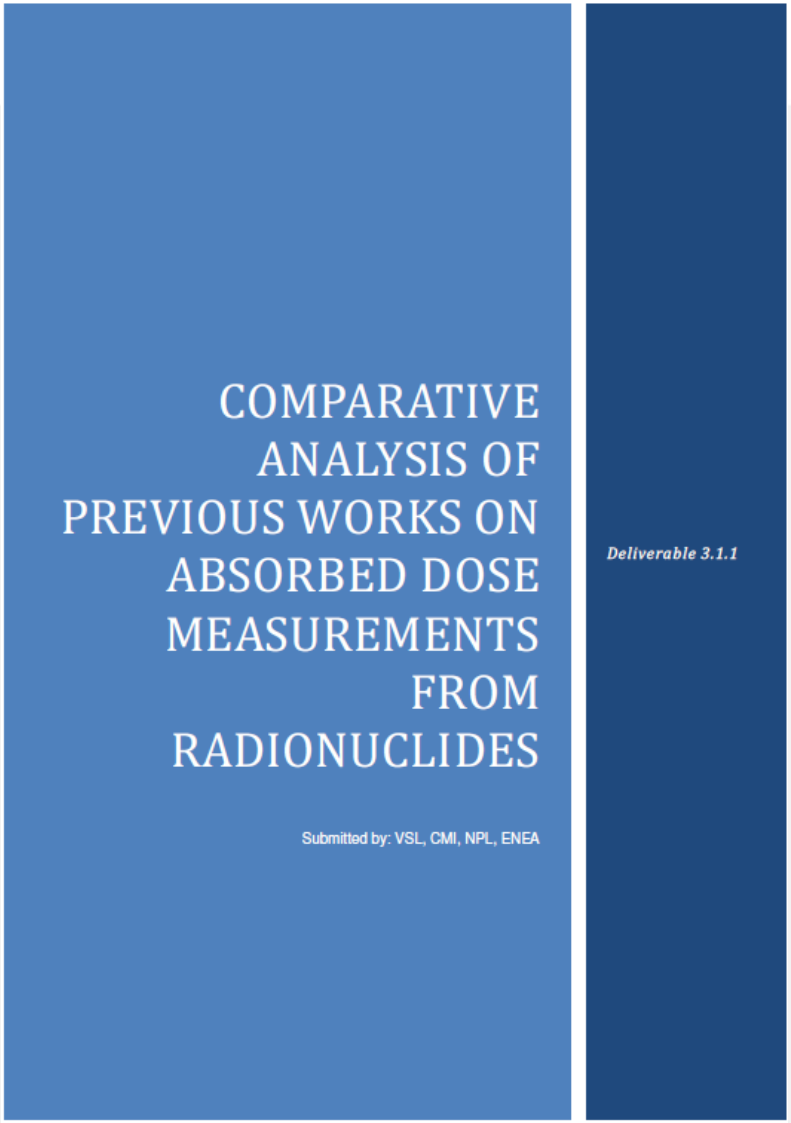
3.1.3: Relevant measurement conditions for clinical dose distribution identified

3.1.4: Absorbed dose measured using dosimeters calibrated against the existing absorbed dose primary standards done

3.1.5: Absorbed dose measurements using the various selected techniques compared and uncertainties analysed

Task 3.1.1: Report

1) Thermoluminescent detectors
2) Autoradiographs
3) MOSFET detectors
4) Diodes
5) Radiochromic Film
6) Gel Dosimeters
7) Alanine and Lithium Formate / EPR systems
8) Liquid Chemical Systems
9) Dyed Polymer Systems



Task 3.1.1:Report

Dyed polymer (PRESAGE™)	Liquid chemical	Alanine	Gel	Film	Diode	MOSFET	TLD	Detector
2% [30]	Dependent on system. 0.5% achievable for Co-60	0.5% for Co-60	4% **	1-2% Co-60 at VSL	1-2%	About 5%, depending on a number of factors. Accuracy decreases as dose increases.	Up to 40%	**Accuracy k=1**
2% [30]	Better than 1%	Better than 1%	4% **	Better than 3%	1%	1-3%		**Precision**
0.2 Gy *	~10 Gy	~5 Gy	gel type dependent FXO: 0.15 Gy TB: 2.5 Gy Polymer gels: 0.1 Gy	0.05 (50 kV x-rays) -100 (Co-60)	Mainly used for dose rate measurements 1.0 cGy/min to 1000 cGy/min	About 1cGy Maximum dose depends on MOSFET lifetime, typically 100-200 Gy	0.002 (mini dosimeter LiF:Mg,Cu,P)-2	**Det limit dose Gy**
max > 50 kGy/h *	N/A	N/A	max > 2 kGy/h	50-400	1.0 cGy/min to 1000 cGy/min	From 0.1 cGy/min	0.005-10	**Det limit dose rate Gy/h**
linear above 2 Gy, "over-response" below 2 Gy [46]	Close to linear response for most systems	Response linear up to ~1 kGy then increasing curvature.	gel type dependent FXO: 15 Gy TB: 150 Gy, linear	About 1% at doses up to 3 Gy	0.1-2% Sensitivity: few nC/cGy	Linear up to tents of Gys, depending on the MOSFET Sensitivity: Few tens of mV per cGy.	2% up to 10 Gy	**Dose response**
2% [46]	Dependent on type of dosimeter	No significant dose rate dependence reported.	4% **	2.5% for 0.5-20 Gy/min	Depends on diode (if n-type or p-type). May be large. Approximately, in the order of 10% for 1.0 Gy/min to 1000 cGy/min	Response with dose rate is generally small.	N.A.	**Dose rate response**
Energy dependent below 200 keV	Dependent on dosimeter type. Generally, slight dependence in megavoltage photon and electron beams. Dependence increases at lower energies.	Slight dependence in megavoltage photon and electron beams. Dependence increases at lower energies.	gel type dependent FXO and TB: not dependent above 100 keV polymer gels energy dependent below 100 keV	5% E<400 kV,2% E>400 kV	Dependence in megavoltage photon and electron beams may be large.	Response with energy may present large variations.	No energy dependence seen for 0.6-6 MeV electrons, strongly energy dependent for low energy electrons (<0.1 MeV) [5]	**Energy response**

Task 3.1.2: Measurement techniques to be used

CMI: response of a Fricke-infused gel with radiochromic xylenol orange ion indicator to a radionuclide solution diluted into the gel.

VSL: measurements of absorbed dose with radiochromic film inside a reference geometry containing a radionuclide solution.

NPL: measurements of absorbed dose using gafchromic film and alanine pellets for small-volume dose measurement.

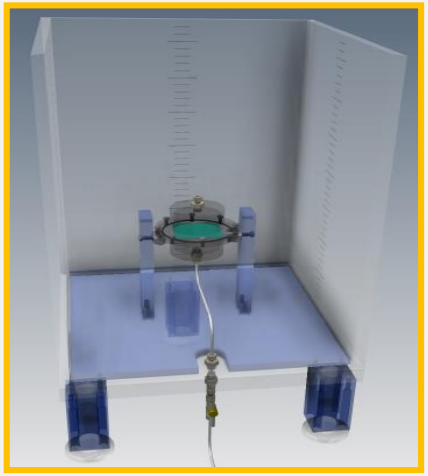
ENEA: measurements of absorbed dose with TLDs inside a reference geometry containing a radionuclide solution.

3.1.3: Relevant measurement conditions for clinical dose distribution identified

	Dosimeter	Calibration method	Phantom material	Radionuclide	Measured quantity
NPL 1	Film		Water/perspex	Y-90, Lu-177	Dose gradient
NPL 2	Alanine	Ir-192	Water/perspex	Y-90, Lu-177	Dose at point/gradient
VSL	Film	Co-60 primary	Perspex	I-131	Dose at point/gradient
CMI	Gel	Co-60 primary	TB/FX Gel	Lu-177	Dose gradient
ENEA	TLD	Co-60 primary	Water	Y-90	Dose at a point

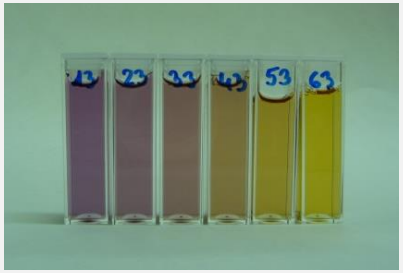
3.1.4: Absorbed dose measured using dosimeters calibrated against the existing absorbed dose primary standards

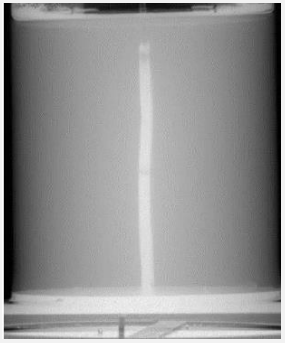
VSL



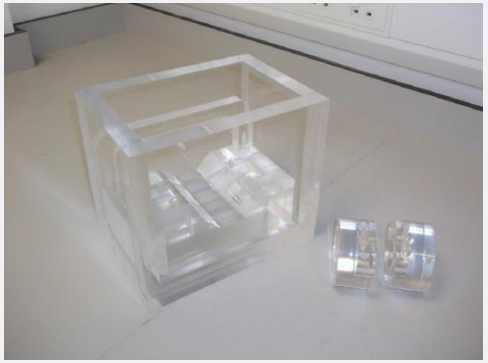
ENEA

CMI





NPL



3.1.4: Absorbed dose measured using dosimeters calibrated against the existing absorbed dose primary standards done→ VSL results

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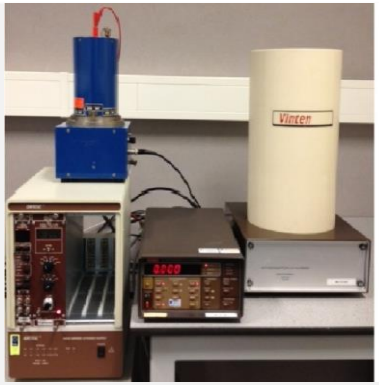
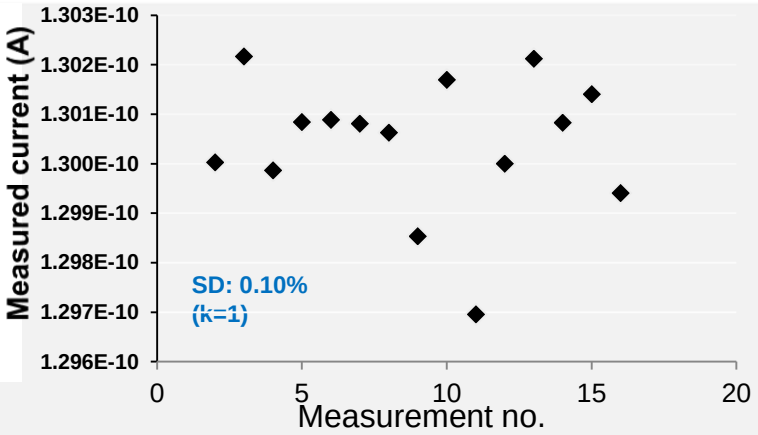
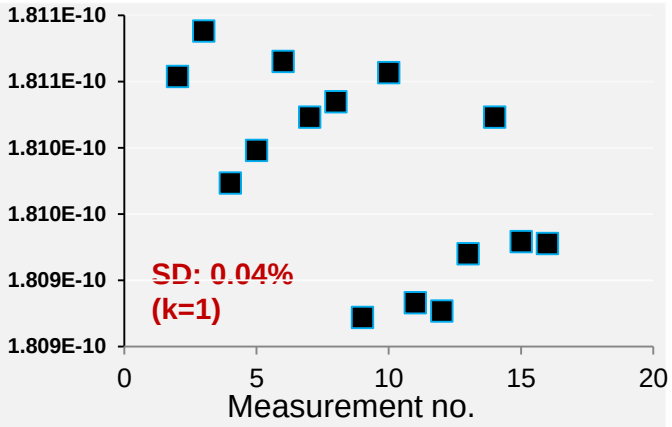
secondary standard



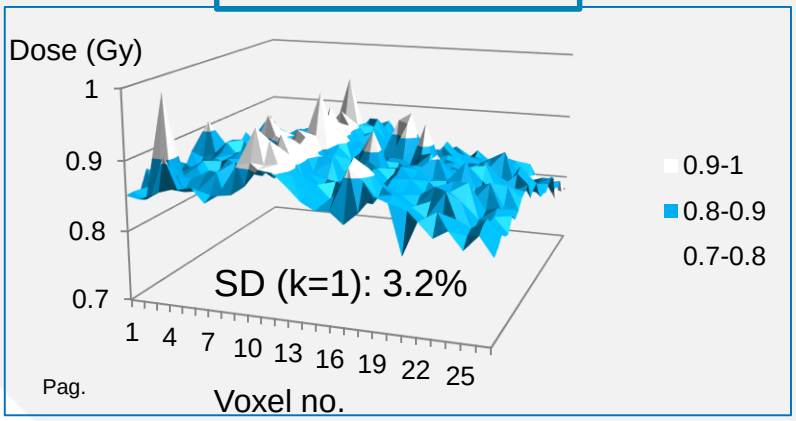
First vial



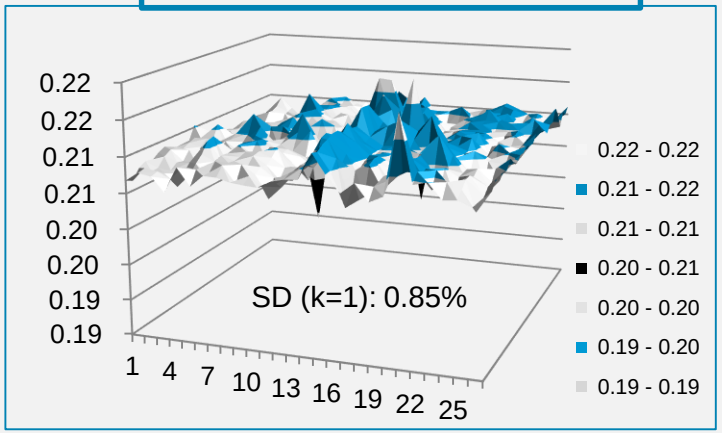
Second vial



Film dosimetry



Pre-irradiation dose



Dutch Metrology Institute

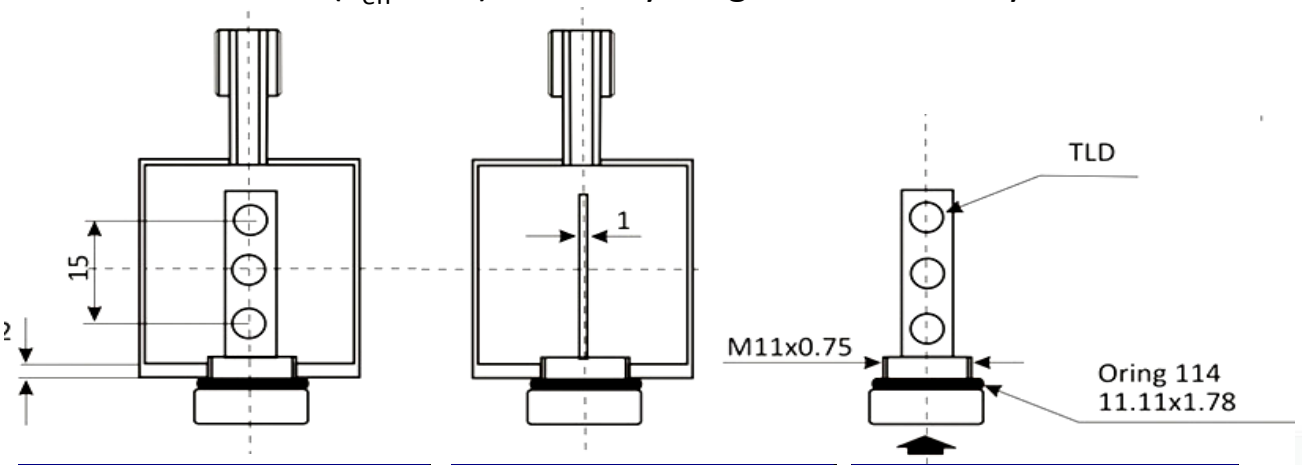
Absorbed dose measurements with LiF(Mg, Cu, P) TL chips in liquid radioactive environment (^{90}Y)

Absorbed dose measurements were performed using LiF(Mg, Cu, P) TL chips immersed in a liquid radioactive solution containing $^{90}YCl_3$. The radionuclide was provided by SIRTeX

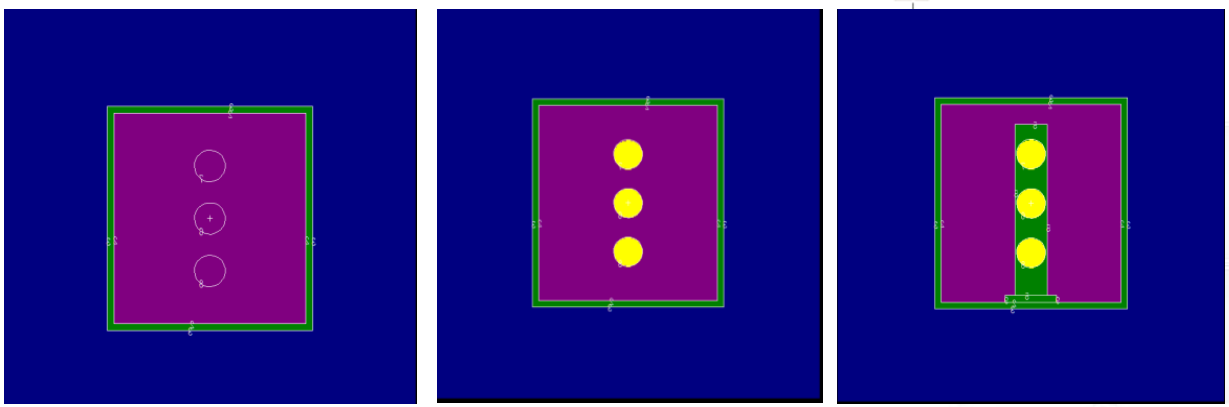
Six cylindrical PMMA phantoms were manufactured at ENEA. Each phantom can host a PMMA stick containing 3 TLD chips encapsulated by a polyethylene envelope. The radioactive liquid environment surrounds the whole stick during the measurement.

TL size: 4.5 mm diameter, 0.8 mm thickness (Z_{eff}= 8.6). Linearity range: 10^{-7} to 10^{2} Gy

Technical drawing of the cylindrical phantom containing ^{90}Y



MC geometry of the cylindrical sample



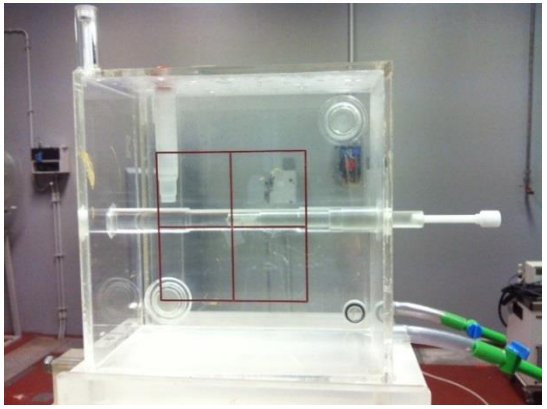
GR-200 LiF(Mg, Cu, P) characterization

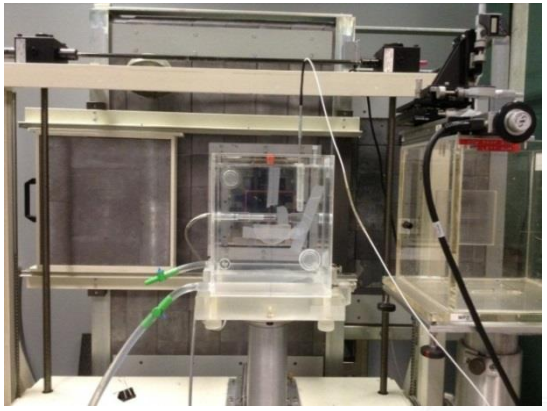
- 100 LiF:Mg,Cu,P chips were characterised in water in a ^{60}Co beam and a subgroup of TLDs with reproducibility below 2.5% was selected.

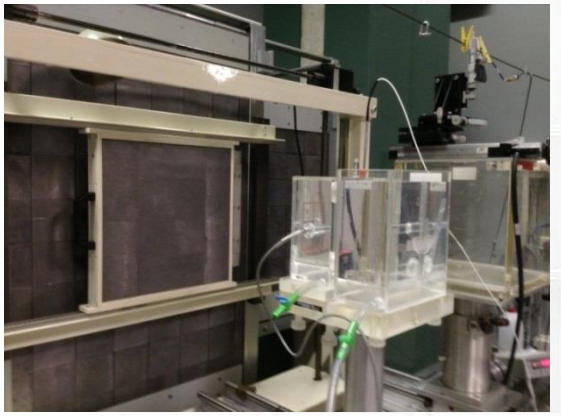
- TLDs were placed into a PMMA holder in water and were calibrated against the absorbed dose to water primary standard (reference ^{60}Co beam with 0.5 Gy dose, dose rate ~ 0.25 Gy/min).

- A 10 cm by 10 cm field size was set and the TLDs were irradiated at a depth of 5 cm in water phantom. This process was repeated three more times and an average calibration factor determined for each TLD.

- The thermoluminescence was measured in a PITMAN/VINTEN TL 654 TOLEDO reader at ENEA-IRP, Bologna (Italy). Each batch of TLDs was annealed before and after irradiation.







Measurements in 90Y radionuclide solution

The absorbed dose to water is obtained considering a number of correction factors evaluated by MC simulations:

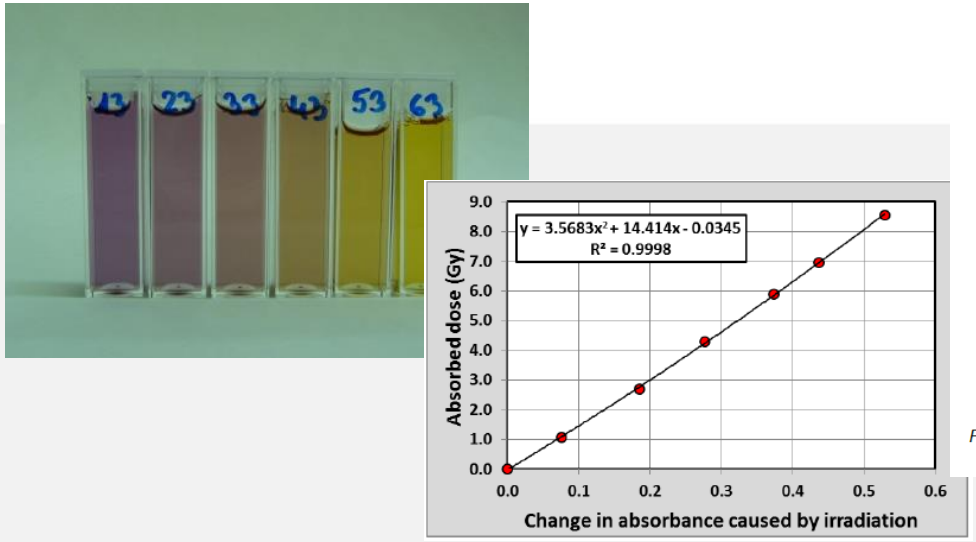
1. Finite volume effect, i.e. the loss of absorbed dose due to exclusion of radioactivity from the volume occupied by the TLD.
2. Correction factor due to the presence of materials other than TLDs.
3. Correction factor due to irradiation geometry and radiation quality different from that used during calibration procedures.

Measurements were performed at IFO hospital (unfunded partner).

A homogeneous ^{90}YCl solution was used, performing activity measurements on site using a portable TDCR. Exposure time was about 30 minutes for each TLD, corresponding to a TLD absorbed dose of about 1 Gy

Data analysis is currently being finalised and final data will be available by the end of April.

3.1.4: Absorbed dose measured using dosimeters calibrated against the existing absorbed dose primary standards CMI results: dose at a point



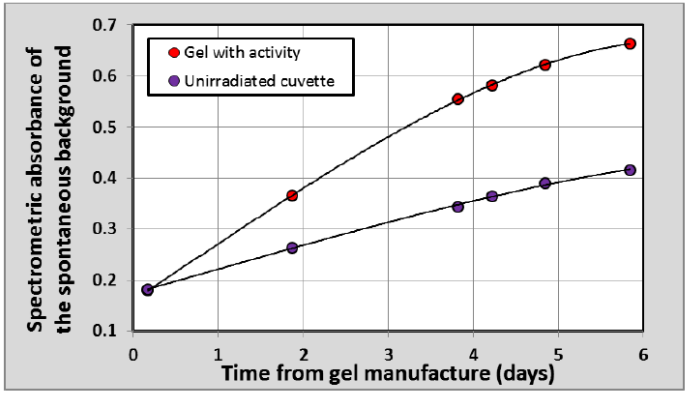
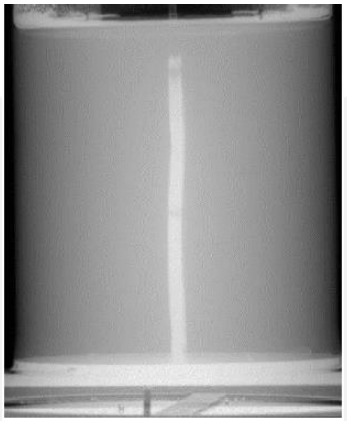


Figure 4: Comparison of increase of the absorbance with time of an unirradiated sample of the first batch of the FX gel (violet) and FX gel sample with Lu-177 radionuclide (red). Black curves represent a polynomial fit.

Table 8: Results of absorbed dose from Lu-177 mixed into the FX gel.

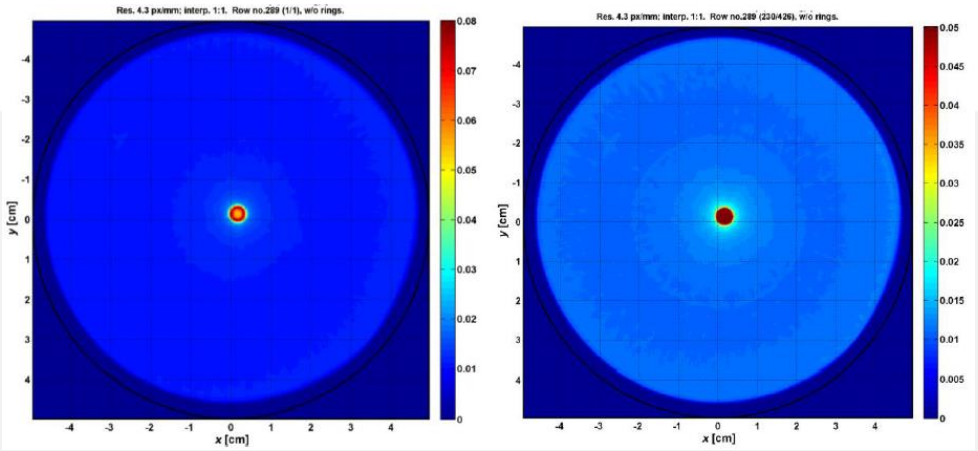
Gel sample	Start of dose integration	End of dose integration	Integration time (hh:mm)	Total change of optical dentity	Spontaneous background increase	Expected dose (Gy)[1]	Measured dose (Gy)[2]	Relative difference [3]
FX batch 1, cuvette 1	26.2.2015 18:01	3.3.2015 10:06	112:05	0.442	0.185	5.106	4.563	-10.6%
FX batch 1, cuvette 2	26.2.2015 18:01	3.3.2015 10:06	112:05	0.442	0.185	5.154	4.563	-11.5%
FX batch 1, cuvette 3	26.2.2015 18:01	3.3.2015 10:06	112:05	0.436	0.185	4.886	4.441	-9.1%
FX gel, batch 2, interval 1	9.3.2015 15:25	10.3.2015 13:00	21:35	0.324	0.015	8.739	8.492	-2.8%
FX gel, batch 2, interval 2	9.3.2015 15:25	10.3.2015 16:49	25:24	0.382	0.015	10.202	9.343	-8.4%

3.1.4: Absorbed dose measured using dosimeters calibrated against the existing absorbed dose primary standards CMI results

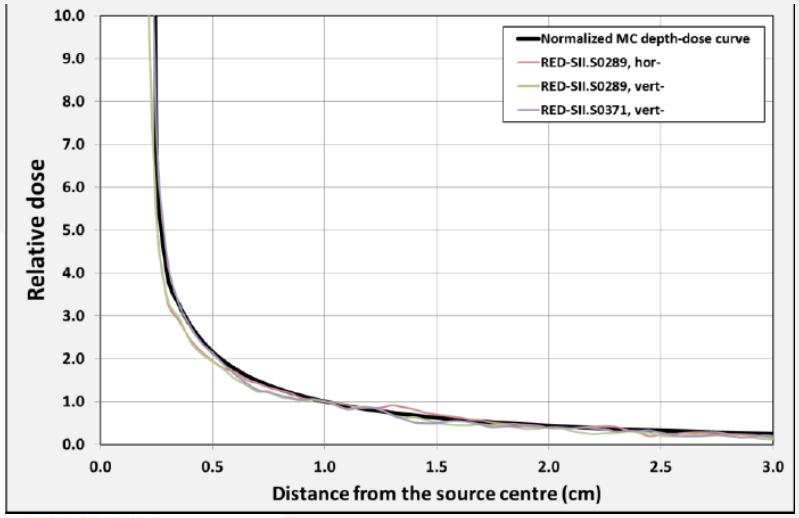


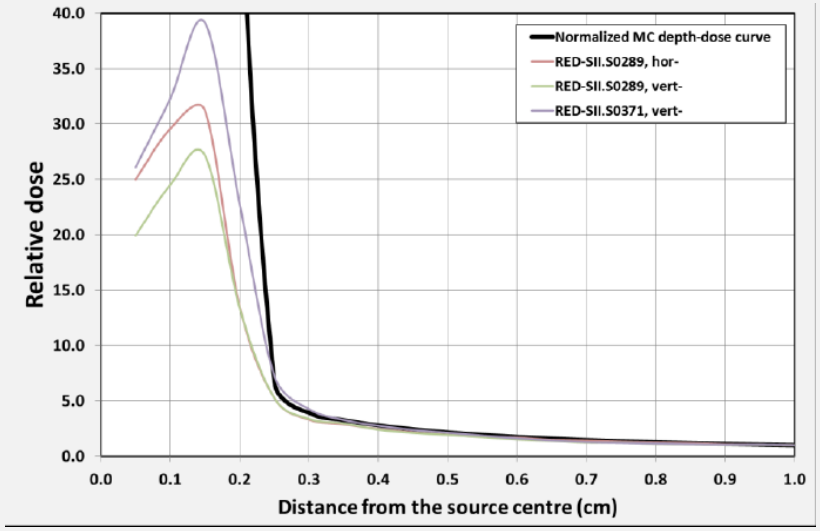
Line source of Lu-177 0.22cm diameter on axis of cylinder filled with gel

Single projection from CCD camera

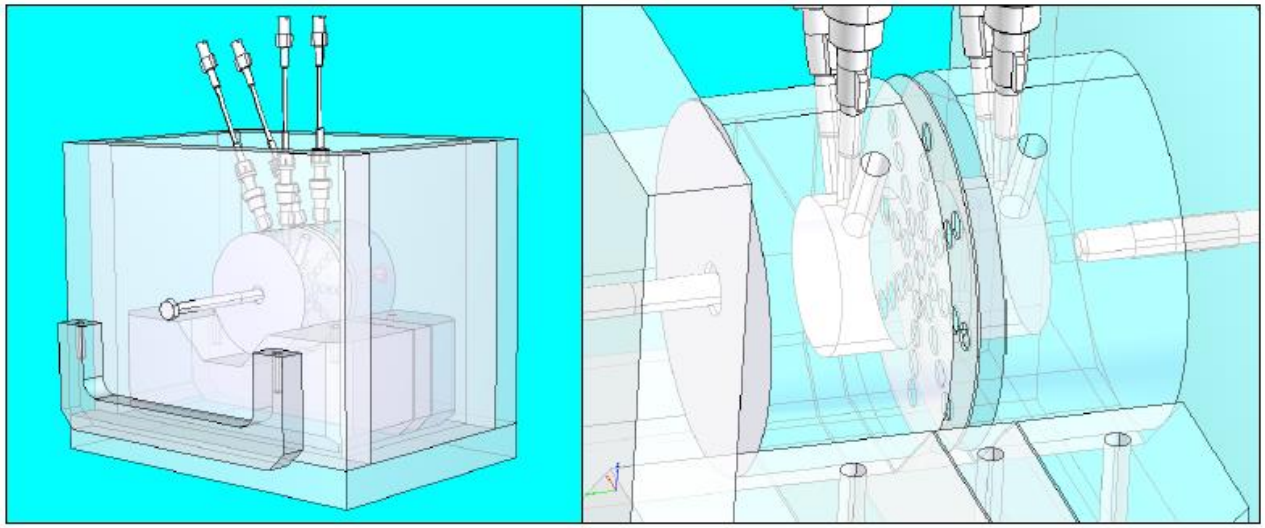


Tomographic reconstruction of dose distribution



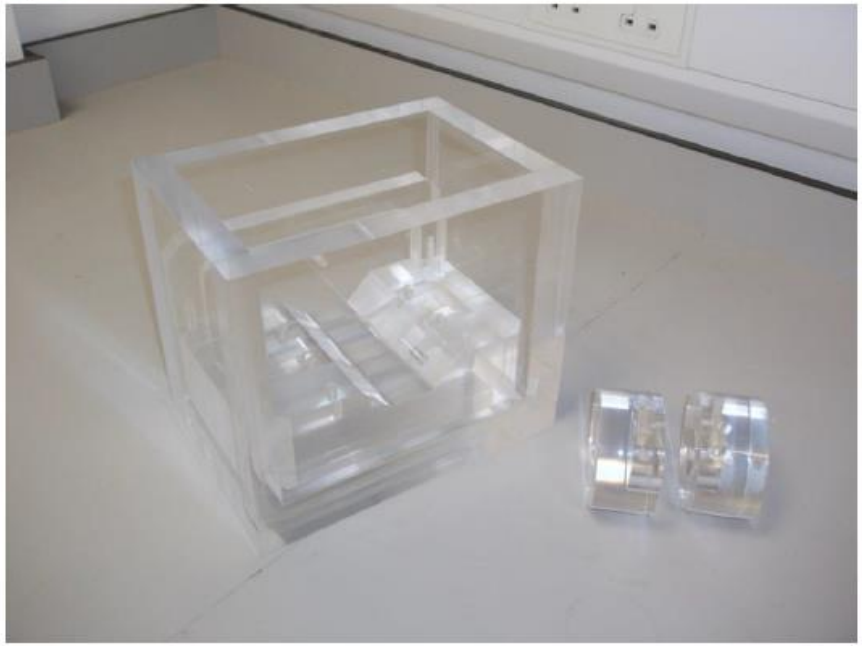


Film/alanine phantom exposer

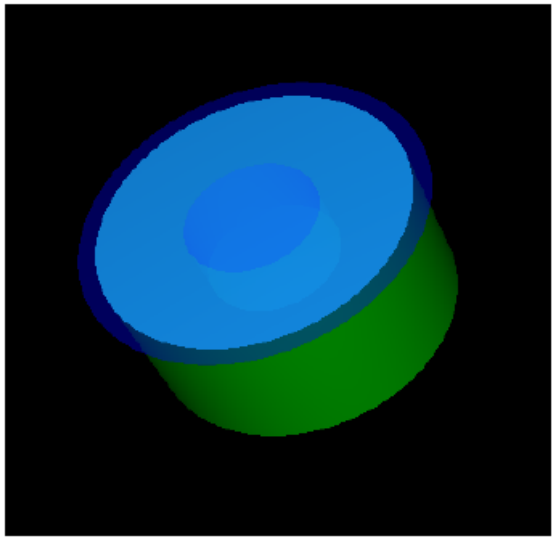


- Material: Perspex
- Wall thickness: 20 mm
- Diameter: 30 mm
- Depth (on each cylinder): 15 mm

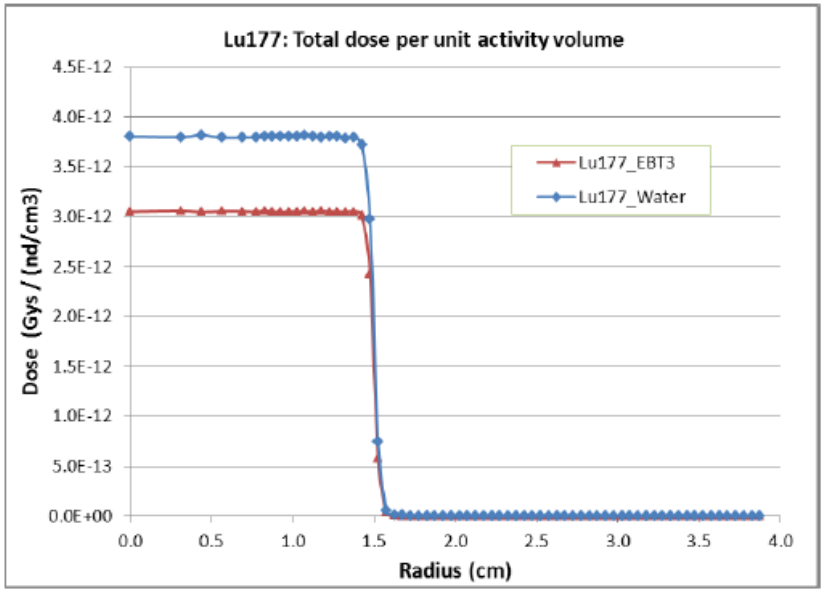
- The film/alanine phantom exposer (three sets) are ready.
- 8 μm Al-Mylar will cover the open ends of both cylinders.
- Extra 6 μm Mylar will laminate the radichromic film and alanine plate (holder) for contamination reasons.

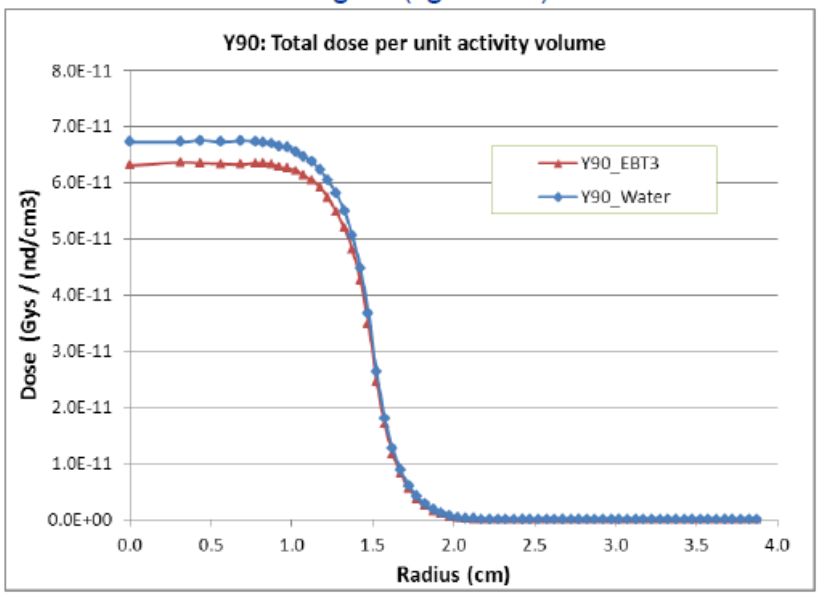


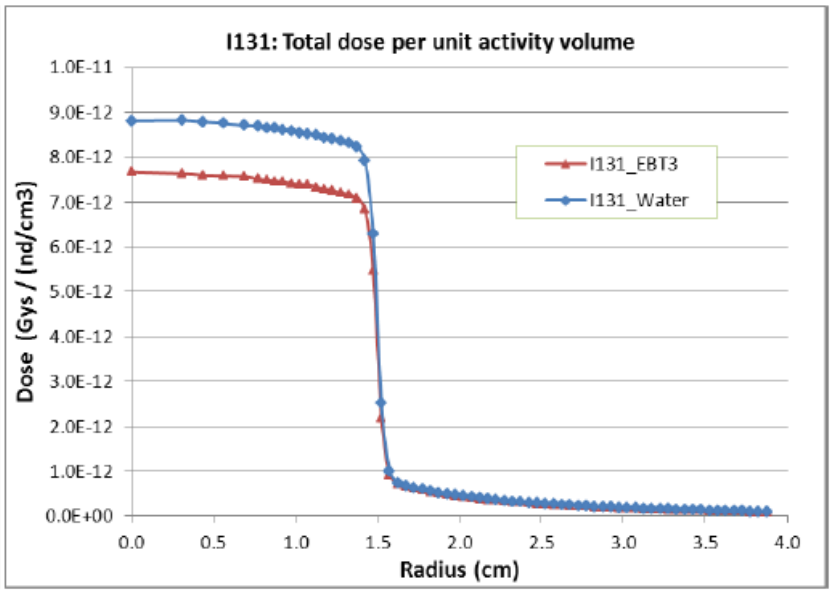
Monte Carlo: EBT-3 film & water



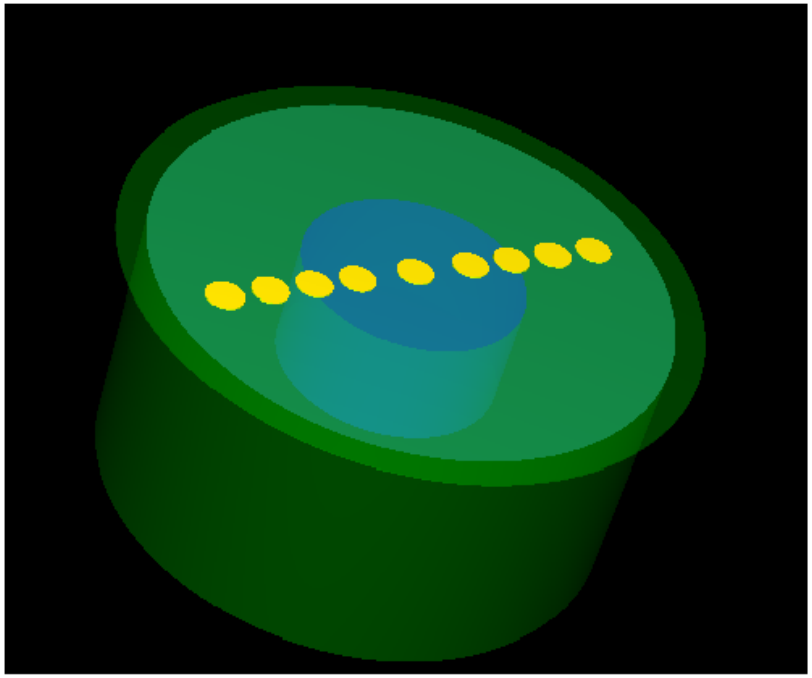
Cross section through model showing film / water region (light blue)



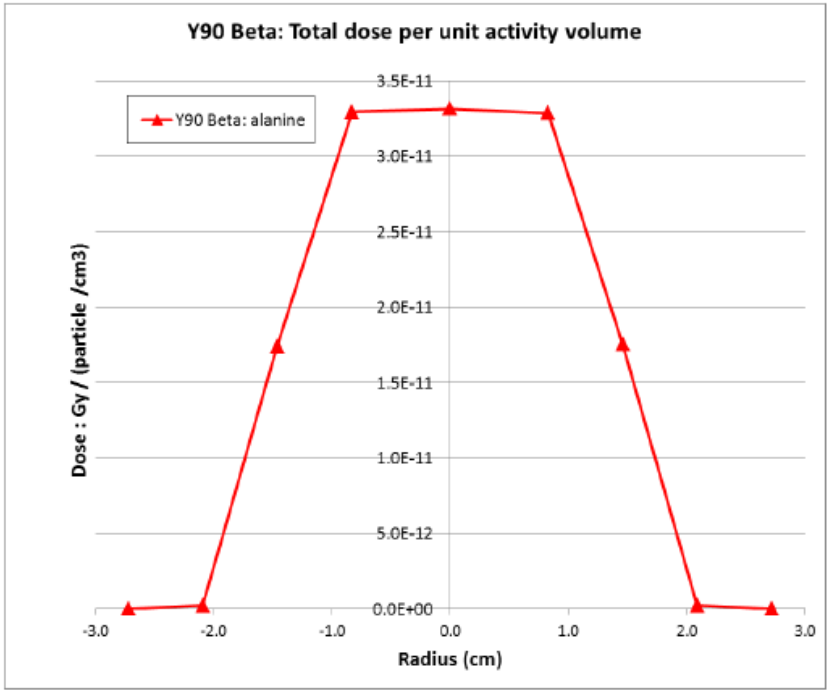




Monte Carlo: alanine



Cross section through model showing alanine pellets (yellow)

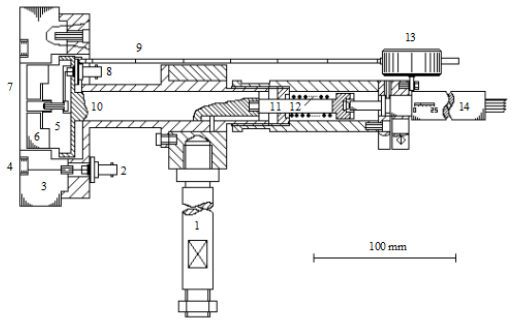


cavity code:

- alanine pellets along radial profile (so far)
- others pellet positions can be added later (e.g. in wall etc)
- Y90 beta spectrum only (so far)

Task 3.2: Feasibility study for the development of a primary absorbed dose standard for radionuclides (ENEA)
Task 3.3: Development of prototype standards based on the feasibility studies from Task 3.2 (ENEA)

- Why?? Metrological legitimacy!
- Feasibility was considered of using calorimetry (ENEA) or an extrapolation chamber (VSL, NPL)
- Calorimetry was assessed as not practical following theoretical considerations and Monte Carlo simulations
- Use of an extrapolation chamber was considered feasible in principle and this has been developed by NPL.



EC container/holder

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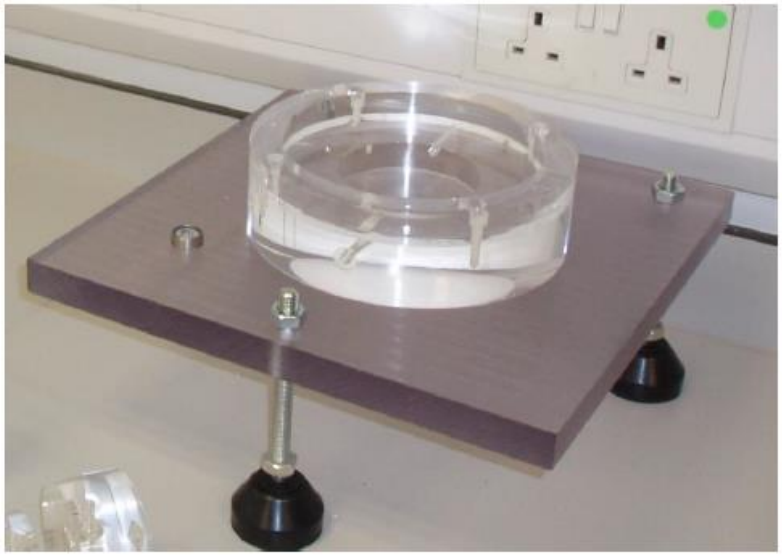
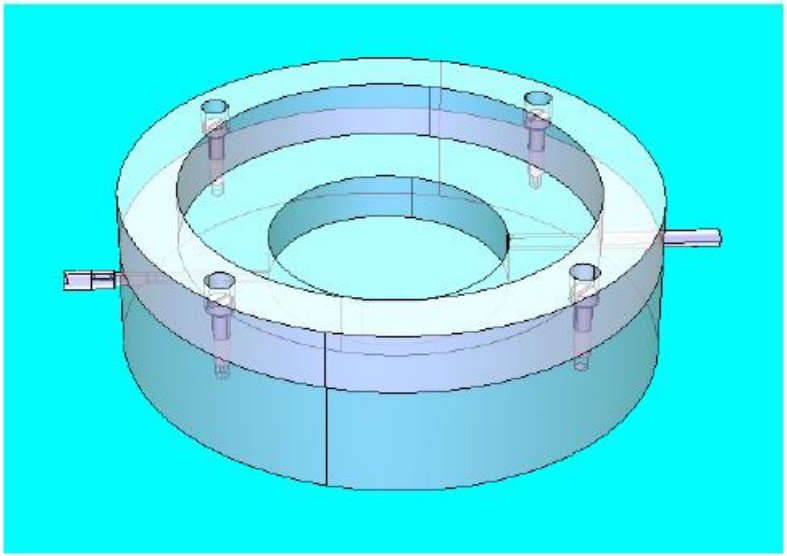
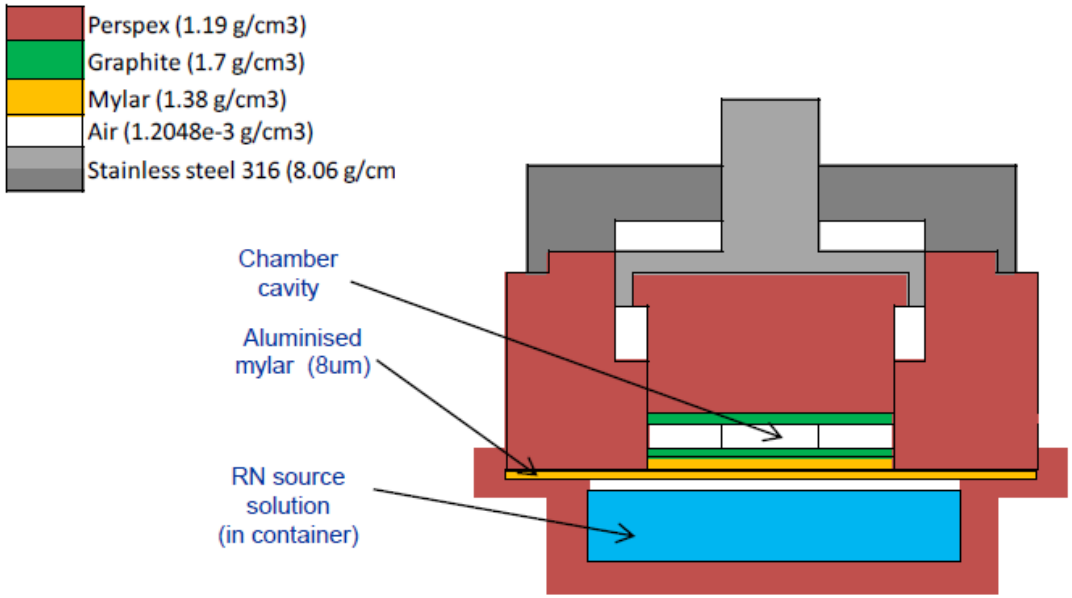


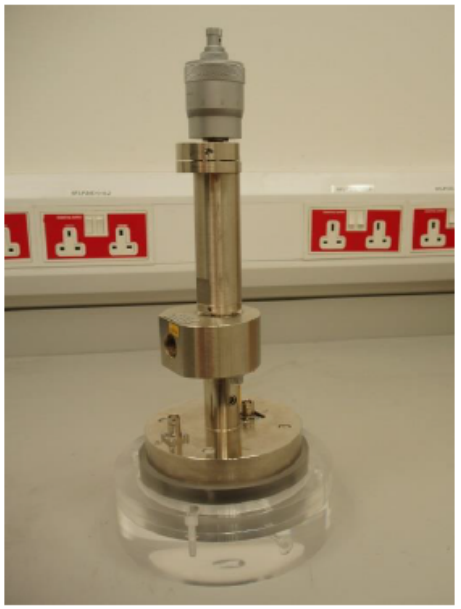


- Three sets of EC container/holder are ready.
- 8 μm Al-Mylar will cover the open end of the container.

- Material: Perspex
- Wall thickness: 20 mm
- Diameter: 80 mm
- Depth: 15 mm

Extrapolation chamber corrections I





- Two **EGSnrc** usercodes:
  - ***cavrznrc*** - dose calculation in a cylindrical / slab (RZ) geometry
  - ***sprrznrc*** - stopping power ratio (SPR) calculation in cylindrical / slab (RZ) geometry
- Simulations for a range of chamber depths (0.1 – 2.0 mm) in various geometries
- RN container: RN solution with 1mm air gap above & 8μm aluminised mylar 'cover'
- Source :
  - *water* in container with uniformly distributed isotropic sources
  - ^{90}Y Beta spectrum only (initially)
- Calculated dose-to-air (Gy/decay) converted to 'current' (nC/decay)
  - typically 0.1% SDOM (type A)

Task 3.4: Assessment and validation of methods for obtaining absorbed dose from cumulative activity (NPL)

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- Investigation of the methods used clinically:
  - OLINDA (MIRD)
  - Dose kernel convolution
  - Monte Carlo
- Comparison between Monte Carlo calculations and physical measurements (using the methods developed in the previous subtasks)
- Investigation of the spread of results resulting from dose calculations on the same data set by different groups using different software and methods (GE, Philips, Hermes, in-house, etc.)
- Recommendations

Workpackage 4:
Modelling and uncertainty analysis

- Task 4.1: Errors and uncertainties in input data and other quantities (NPL)
- Task 4.2: Modelling and uncertainty evaluation (NPL)
- Task 4.3: Ramifications of modelling and uncertainty (NPL)

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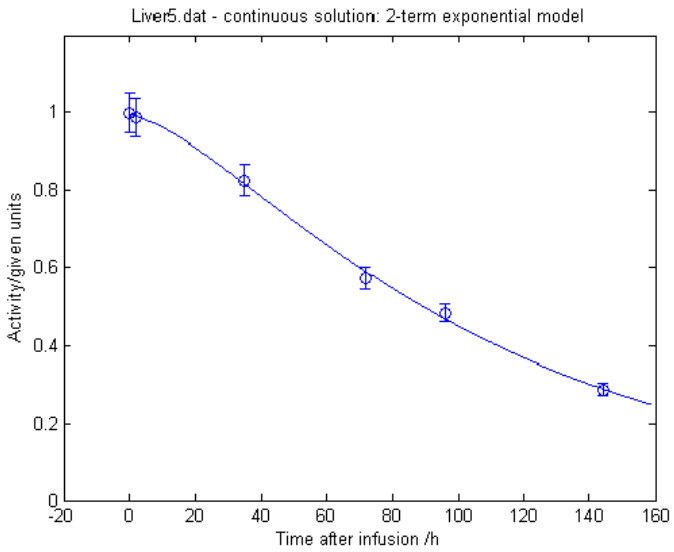
Task 4.1: Errors and uncertainties in input data and other quantities

- Analysis of the uncertainties in the time-activity curve resulting from choice of measurement time points and interpolation/extrapolation method



- The uncertainty in each of the links in the measurement chain is quantified in terms of standard uncertainty.
- Recognized international guidance on uncertainty propagation applied to yield absorbed dose standard uncertainty

Task 4.2: Modelling and uncertainty evaluation

Propagation of uncertainty in each step of the dose calculation to give uncertainty associated with mean absorbed dose value when measured at the organ or tumour level

Two cases modelled:

Whole-body (WB) dosimetry for personalized treatment planning of ^{131}I-MIBG radionuclide therapy for neuroblastoma (data: ICR)

Absorbed doses for liver, spleen, kidneys and lesions carried out with accompanying uncertainty analysis for 32 patients undergoing ^{90}Y-DOTATATE therapy with ^{111}In-SPECT imaging (data: ICR)

Task 4.3: Ramifications of modelling and uncertainty

Investigation of relative importance of links in metrology chain

Comparison of merits of different dosimetry methodologies currently in use

Indications of ramifications for patient outcomes and clinical research resulting from reducing $u(D)$

And . . .

Lena Johansson will tell you about Workpackages 1 and 2 this afternoon, and recommendations and guidelines that will follow from the project

The round table discussion at the end of tomorrow will be an opportunity to talk about what metrology laboratories can do next for MRT dosimetry

A big thank you to everyone who has worked for the MetroMRT project.

And thank you for listening!

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