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IRSN
INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

RADIATION PROTECTION FOR NEW RADIONUCLIDES IN NUCLEAR MEDICINE

20th EAN workshop – 3 October 2023

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Session 3: Focus on (new) radiopharmaceuticals

Disclosure of Interest Statement

My co-authors and I have nothing to disclose

Context

- Strong development of new radionuclide therapies (and diagnostics) : Lutetium-177, Actinium-225, etc.
- French Nuclear Safety Authority (ASN) asked IRSN in 2020 to perform 4 studies on these new radionuclides
- Aim : anticipate the radiation protection issues for the new radionuclides

Performed studies

- Advanced study on new radionuclides:
  - Promising radionuclides for human use and clinical application perspectives in France
  - Vectors and diagnostic/therapeutic applications
  - Biological patient data

→ April 2020 → February 2021: 1st report

- Patient RP (individual treatment planning) and RP of relatives ;

→ →June 2021: 2nd report

- Occupational RP:
  - Health establishments
  - Outside health establishments : liquid radioactive waste

+ case of patient death after NM procedure

→ → October 2021: 3rd report

→ → January 2023: 4th report

1. Advanced study on new radionuclides

Method

To establish the list of promising radionuclides:

- Meetings with 14 stakeholders in NM:
  - France:
    - Competitive clusters
    - Radionuclide production research institutions
    - Nuclear medicine department
    - Professional bodies
    - Medicines/health products Agency
  - Europe: EANM, Nuclear Medicine Europe, MEDraysintell, HERCA
  - International: IAEA
- Identification of influence factors for the clinical development of new radionuclides and indicators (e.g. number and stage of clinical trials)
- Classification about the probability of clinical use in France

Classification of new radionuclides

1=sure (Marketing authorization in France), 2=very likely, 3=likely, 4=unlikely

Very subjective point of views according to the stakeholders: research **vs** clinic

Diagnostic

RN	Modality	Category
^{68}Ga	TEP	1
^{82}Rb	TEP	
^{64}Cu	TEP	2
^{89}Zr	TEP	
^{43}Sc	TEP	3
^{44}Sc	TEP	
^{62}Cu	TEP	
^{117m}Sn	SPECT	
^{124}I	TEP	
^{75}Se	SPECT	4
^{152}Tb	TEP	
^{155}Tb	SPECT	
^{203}Pb	SPECT	

Therapy

RN	Modality	Category
^{177}Lu	β	1
^{223}Ra	α	
^{166}Ho	β	2
^{225}Ac	α	
^{47}Sc	β	3
^{67}Cu	β	
^{161}Tb	β	
^{188}Re	β	
^{211}At	α	
^{212}Bi	α	
^{212}Pb	α	
^{213}Bi	α	
^{227}Th	α	
^{149}Tb	α	4

« α » = α-emitters or with an α-emitter in the filiation

2. RP for patients and their relatives

Individual treatment planning: Method

IRSN performed a study on individual treatment planning:

- regulatory context
- dose-response studies
- ressources required
- professionals position
- pro/cons arguments

Individual treatment planning: Results (1/2)

Regulatory basis:

Marketing authorization: fixed activity

VERSUS

2013/59/EURATOM Dir.: Art. 56 « optimisation »

For example, Lutathera's (^{177}Lu-DOTATATE) Summary of Product Characteristics:

Posology

> The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7 400 MBq each.

Dose-response studies from the manufacturers:

> The applicant did not submit dose-response studies.

(Lutathera's Assessment report)

https://www.ema.europa.eu/en/documents/assessment-report/lutathera-epar-public-assessment-report_en.pdf

Individual treatment planning: Results (2/2)

- Resources required :
  - Personnel (trained and available)
  - Equipment: activimeters, software
  - Clinical dosimetry protocols

- Many professionals are in favor of the individual treatment planning (articles published++) and many others are against

- Pro/cons arguments found in the litterature, for example in a EC report (Konijnenberg, RP 194) :

Objections to individualised therapy	Solutions
Time and resource consuming	Reimbursement for dosimetry studies
Inconvenient for the patient	Keep it practical and relevant
On-site expertise needed	Medical physics expert support mandatory
No established dosimetry method	Benchmarks for dosimetry software
Unclear dose-response models	Focussed radiobiology research in MRT
Large uncertainties in absorbed dose	Improve accuracy in dosimetry process
Safe activity from clinical trials / experience	Dose response model guided clinical trials
One size fits all is more convenient	Sub-optimal patient care is not acceptable

Individual treatment planning: Results (3/3)

- Results of the analysis: work still needed on regulatory and research aspects

→ IRSN made several proposals that could unlock the situation

Individual treatment planning: IRSN's proposals (1/2)

Regulatory ambiguities → IRSN proposals:

- check with the authorities and scientific/professional bodies whether it is possible to include dosimetry-based administration (not just fixed dosage) in Summary Products Characterisitcs
- encourage clinical trials with new NRs to include a dosimetric component to gain a better understanding of the dose-effect relationship
- clarify the involvement of medical physicists in NM departments performing RN therapy

Improve knowledge of radiobiology → IRSN proposals:

- obtain cell survival curves and dose-effect relationships in animals, and compare them with external radiation (reference)
- study (in vivo/vitro) the effect of dose rate and non-uniform distribution of activity as well as modulators of the response to radiation (e.g. stimulation of the immune system)

Individual treatment planning: IRSN's proposals (2/2)

Consolidate knowledge of dose-response relationships → IRSN proposals:

- Systematically assess doses in clinical trials
- harmonize/develop dosimetric practices
- use high-performance dose calculation software
- have resources in terms of personnel trained in dosimetry.

+ Create databases or registers of NM procedures (imaging + treatments) for *a posteriori* studies (dose assessments/biokinetics to obtain reliable data on dose-effect relationships)

RP of relatives (after RN therapy)

- Calculation principle:
  - Dose rate around patient at the moment of release, and its decay with time
  - Exposure scenario: frequence, time frame, and contact distance

- IRSN developped a dose calculation method for relatives:
  - 1- choice among scenarios and calculation methods already published
  - 2- improvement of the model for dose rate decay

    mono-exponential → bi-exponential (more adapted for out-patient treatments)
  - 3- checking results with test calculations

- Calculation of doses likely to be received
  → contact restriction times

RP of relatives (after RN therapy)

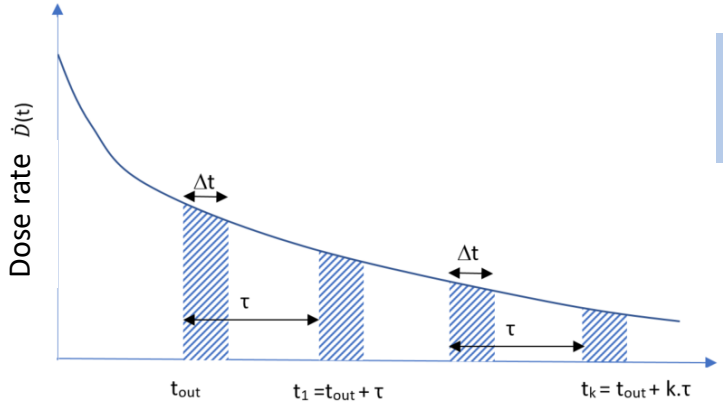
Bi-exponential model:

$$D_{bi} = \frac{\dot{D}_{out} k_d}{(f_r e^{-\lambda_r t_{out}} + f_l e^{-\lambda_l t_{out}})} \left(\frac{f_r}{\lambda_r} \frac{1 - e^{-\lambda_r \Delta t}}{1 - e^{-\lambda_r \tau}} e^{-\lambda_r t_{out}} e^{-\lambda_r d_{res}} + \frac{f_l}{\lambda_l} \frac{1 - e^{-\lambda_l \Delta t}}{1 - e^{-\lambda_l \tau}} e^{-\lambda_l t_{out}} e^{-\lambda_l d_{res}} \right)$$

Fixed by the « maximal » retention and release date : known

Normalization by dose rate measurement

Correction for distance



RP of relatives (after RN therapy)

Results strongly depends on input parameters:

- Biokinetics: decay model
- exposure scenario
- dose constraints: by administration **vs** whole treatment
- initial dose rate
- etc.

☑ Validation of the model:

Results consistent with those from 2 articles, using the same input parameters

(Carlier et al. 2004 doi: 10.1051/radiopro:2004012. / Levart et al, 2019 doi: 10.1186/s40658-019-0243-1.)

RP of relatives (after RN therapy)

- Calculation method applied: ^{177}Lu et ^{166}Ho
- Order of magnitudes **according to input parameters:**

Restriction time	^{177}Lu	^{166}Ho
Adults	~10 days	Some days
Children	~15 days	~1 week

Input parameters:

	^{177}Lu	^{166}Ho
Dose rate @1m, at the moment of release	15 µSv/h	60 µSv/h (« maximal » value considered)
Dose constraints	3 mSv (adults) et 1mSv (enfants) for the whole treatment (4 administrations for ^{177}Lu and 1 administration for ^{166}Ho)	

Actions following the IRSN study

- IRSN calculator initially developped for ^{177}Lu et l'^{166}Ho for this study, then completed for other common therapies: ^{131}I and ^{90}Y

- Publication in open access: Journal of Radiological Protection (SRP Society of Radiological Protection), along with the Excel calculation file in supp. material

https://iopscience.iop.org/article/10.1088/1361-6498/acc4d1

- WG radioprotection of the French Society of Nuclear Medicine (SFMN)
  - development of a calculator in collaboration with the French Society of Medical Physics (SFPM)

- Objective: unique calculator in use in French NM departments, that takes the advantages of both

3. Occupational RP in case of patient death

Occupational RP in case of patient death: Objectives

- Assessment of the doses which could be received:
  - by undertakers : transport and embalming of the body
  - by crematorium staff

Transport and embalming: Method

- Most promising therapeutic radionuclides considered: Lu-177, Ra-223, Ho-166 et Ac-225

$$H^*(10) = \dot{H}^*(10) \cdot \Delta t = \frac{\Gamma \cdot A \cdot d_{réf}{}^2}{d^2} \cdot e^{\frac{-\ln(2)\cdot t_1}{T_{eff}}} \cdot e^{\frac{-\ln(2)\cdot t_2}{T_{phy}}} . \Delta t \leq 300\ \mu Sv$$

before death | after death

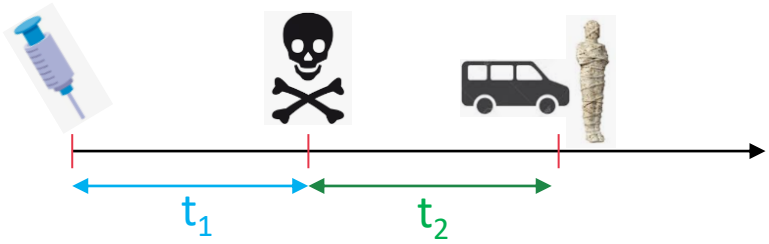
Hyp : 3 deceased patients/year (< 1 mSv/year)

- Hypothesis for time and distance :
  - Transport : 1 h at 50 cm
  - Embalming : 2 h at 50 cm

✓ *Hypothesis validated by funeral personnel*

- Administered activities, equivalent dose rate constant et effective half-lives : values from literature with conservative approach

Transport and embalming: Results and conclusion



$$\frac{\Gamma \cdot A \cdot d_{réf}{}^2}{d^2} \cdot e^{\frac{-\ln(2)\cdot t_1}{T_{eff}}} \cdot e^{\frac{-\ln(2)\cdot t_2}{T_{phy}}} \cdot \Delta t \quad \leq 300\ \mu Sv$$

	Immediate death after administration t_1=0		**No constraints after death t_2=0**
	t_2 min = ?		**t_1 min = ?**
	transport	embalming	
Ra-223-dichloride	-	-	-
Ac-225-PSMA	-	-	-
Lu-177-DOTATATE		4 days	0,5 day
Lu-177-PSMA	-	4 days	1 day
Ho-166 microspheres	1 days	2 days	1,3 day
I-131 iodide (3,7 GBq)	11 days	19 days	2,1 days
I-131 MIBG (7,4 GBq)	19 days	27 days	6,6 days

Regulation ✓

Crematorium staff exposure: Method

- Therapeutic RN considered: Cu-67, Y-90, In-111, I-131, Sm-153, Ho-166, Er-169, Lu-177, Re-186, Re-188, At-211, Pb-2012, Bi-212, Bi-213, Ra-223, Ac-225

- Visits in 3 crematoria to understand the operations carried out according to the type of fume filtration system (small vs. large container)

- Staff:
  - technical (in charge of cremation)
  - administrative (office)
  - external technician (large container maintenance)

- Protection considered: walls + PPE

- Activity considered : Activity administered to the patient without any decay (most conservative assumption)

Crematorium staff: Results and recommendations (1/2)

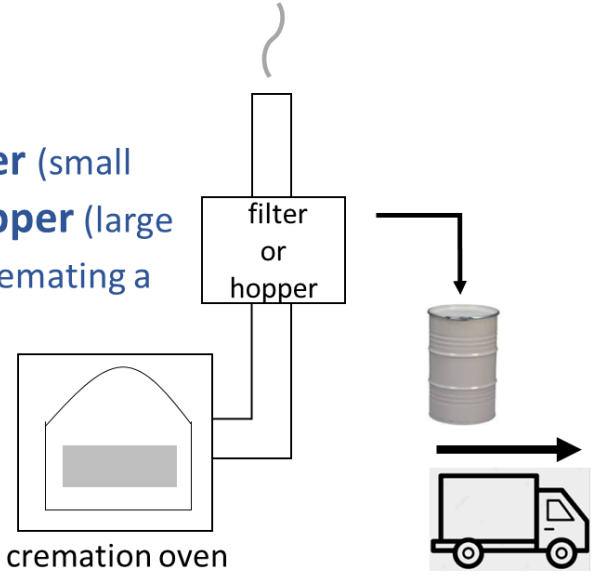
- Only a few cases lead to more than 300 µSv for I-131, Ac-225 and In-111 (therapeutic application) in some scenarii (e.g. external technician)

- To reduce exposure, IRSN recommends:
  - for I-131, to increase the time between death and cremation as much as possible, in compliance with national regulations and with the family's agreement
  - every effort should be made to inform the crematorium of the radioactive nature of the body, so that recommendations can be applied

Crematorium staff: Results and recommendations (2/2)

Even in the worst-case scenario, application of the 3 recommendations below will drastically reduce worker exposure to below 300 µSv :

❶ : **empty** the **filter** (small container) or the **hopper** (large container) **before** cremating a radioactive body



❷ : **evacuate the drum** containing the contaminated dust **as quickly as possible**

❸ : If ❶ and ❷ not possible, **increase the distance** between the contaminated filter storage area and the other rooms in the crematorium (in particular the administrative rooms)

General conclusion

IRSN's studies in line with current European concerns:

- Consistency of the new radionuclides identified by IRSN with a NUC ADVISOR report (on behalf of the EC)

  "Co-ordinated Approach to the Development and Supply of Radionuclides in the EU", N°ENER/D3/2019-231 - Final Report

- European project " SIMPLERAD" whose objective is "to improve the understanding of the **links** and the **inter-dependencies** between the European **pharmaceutical legislations** and the **Euratom** radiation protection requirements" https://earl.eanm.org/simplerad

- HERCA WG Medical application, in particular the WP Nuclear Medicine, work on the radiation protection issues in radionuclide therapy:

Article "Radiation safety of current European practices of therapeutic nuclear medicine: survey results from 20 HERCA countries", Bly R. et al, DOI:10.1088/1361-6498/acafef

Thank you for your attention.

Reports available, in French, on:

Nouveaux radionucléides en médecine nucléaire pour des actes à visées diagnostique, ou thérapeutique (irsn.fr)

and

https://www.irsn.fr/sites/default/files/2023-02/Avis-IRSN-2023-00004.pdf
(patient death/cremation)