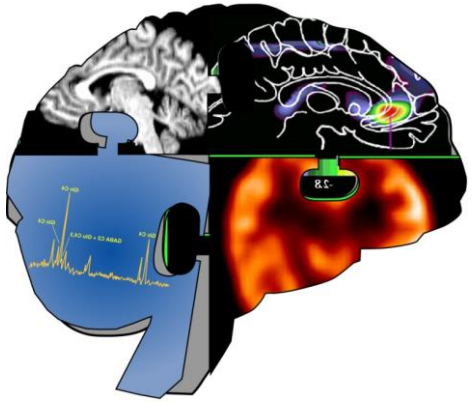


National Institute
of Mental Health

Dosimetry for first-in-human PET studies
The NIH experience

Paolo Zanotti Fregonara, M.D., Ph.D.

Molecular Imaging Branch, National Institute of Mental Health,
Bethesda, Maryland

Medical Imaging Drugs Advisory Committee; August 1st, 2023

Main points

- Animal dosimetry is resource-intensive and poorly predicts human values
- Human dosimetry is expensive, and the tracer may not work
- The dose of a ^{11}C tracer is predictable and primarily based on the half-life of ^{11}C

Proposed solutions:

- Abandon animal dosimetry for both ^{18}F and ^{11}C
- Postpone human dosimetry until the tracer is proven to work
- Abandon human ^{11}C dosimetry scans and use an average dose

Traditional NIH pathway for first-in-human studies

1) Perform dosimetry in monkeys (preferred animal model at the NIH)

2) Perform dosimetry in humans

3) Evaluate the validity of the new tracer (e.g., with brain studies)

Pathway for ^{11}C and ^{18}F first-in-human studies

Eur J Nucl Med Mol Imaging (2012) 39:544–547
DOI 10.1007/s00259-011-2005-8

LETTER TO THE EDITOR

Suggested pathway to assess radiation safety of ^{11}C-labeled PET tracers for first-in-human studies

Paolo Zanotti-Fregonara · Robert B. Innis

Eur J Nucl Med Mol Imaging (2013) 40:1781–1783
DOI 10.1007/s00259-013-2512-x

LETTER TO THE EDITOR

Suggested pathway to assess radiation safety of ^{18}F-labeled PET tracers for first-in-human studies

Paolo Zanotti-Fregonara · Adriaan A. Lammertsma · Robert B. Innis

1. Abandon animal dosimetry
2. Begin with whole-body scanning in a single human subject using a low activity
3. To determine whether the radioligand is worth pursuing, then do scans centered on the organ (e.g., brain)
4. If the radioligand looks promising, complete the human dosimetry study

Proposal to abandon ^{11}C dosimetry

HOT TOPICS

^{11}C Dosimetry Scans Should Be Abandoned

Paolo Zanotti-Fregonara[1], Adriaan A. Lammertsma[2], and Robert B. Innis[1]

[1]Molecular Imaging Branch, National Institute of Mental Health, Bethesda, Maryland; and [2]Department of Radiology and Nuclear Medicine, Amsterdam UMC, VUmc, Amsterdam, The Netherlands

1. Abandon both animal and human dosimetry for ^{11}C tracers
2. Use an average Effective Dose (5 µSv/MBq)

Monkeys poorly predict human dosimetry

- Dosimetry from human and nonhuman primates is available for 16 ^{11}C tracers and 21 ^{18}F tracers

- Effective dose
  - Monkey scans unpredictably under- or overestimated the human effective dose (mean absolute percentage difference of 31%)

- Organ dose
  - In only one third of the tracers was the target organ the same in both monkeys and humans
  - The dose poorly predicted the human dose (mean absolute difference of 42%)

Mice and piglets poorly predict human dosimetry

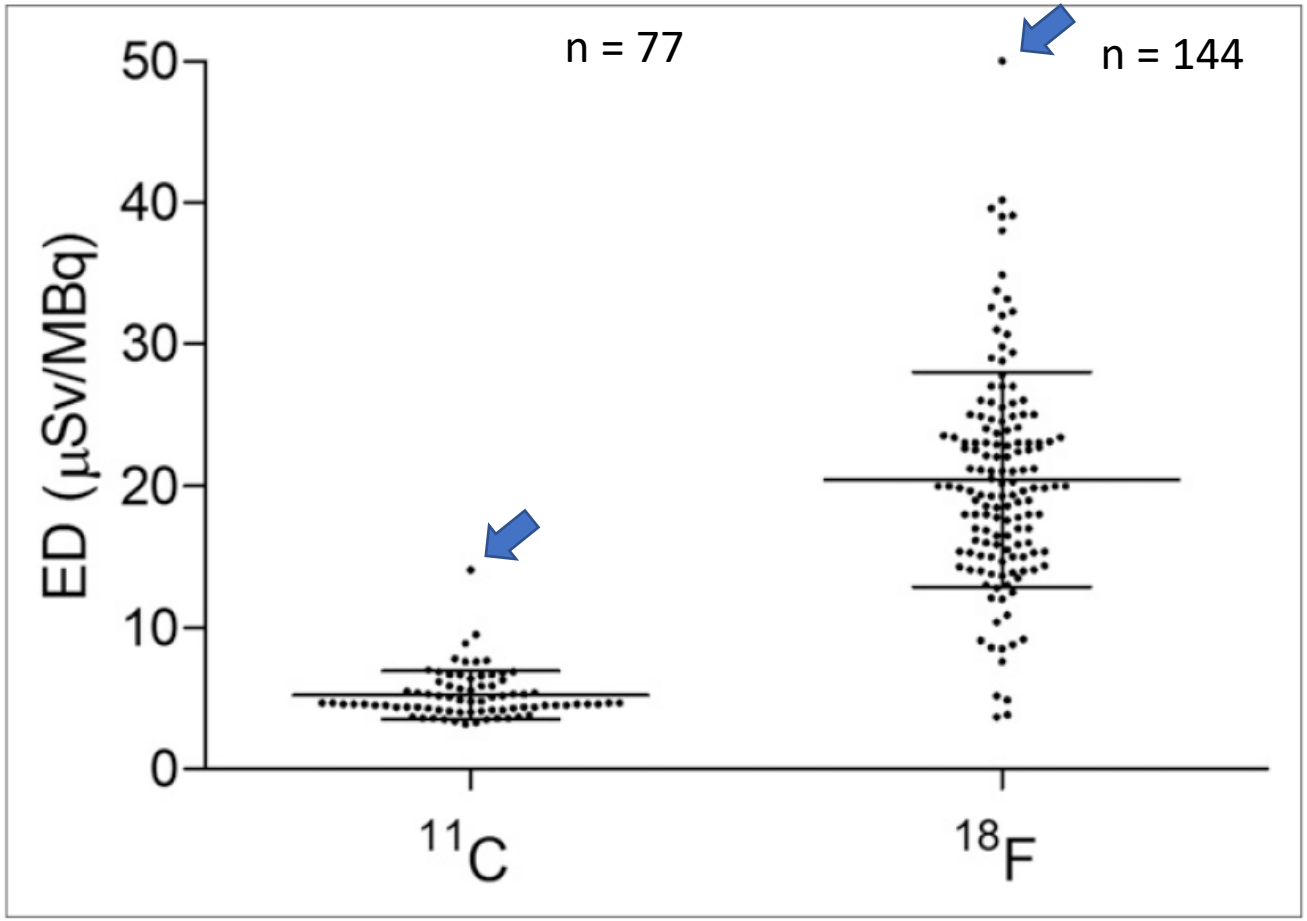
-the German experience

- Animals underestimate the dose to humans by up to 40%

- E.g., Effective Dose for [^{18}F]Flubatine
  - 12.5 µSv/MBq in mice
  - 14.7 µSv/MBq in piglets
  - 23.4 µSv/MBq in humans

[^{18}F]FACH Sattler *Molecules* 2020
[^{18}F]Flubatine Sattler *J Nucl Med* 2014

Dose values calculated in humans are similar among tracers (especially ^{11}C)



Average dose = 5 µSv/MBq 20 µSv/MBq

Variability can be largely explained by methodological choices

A faster voiding with a dynamic bladder model would reduce:

Effective dose of ^{11}C-flumazenil by 13% and of ^{18}F-CP-18 by 61%

Bladder dose of ^{11}C-flumazenil by 33% and of ^{18}F-CP-18 by 74%

Laymon *Mol Imaging Biol*. 2012
Doss *J Nucl Med*. 2013

Human dosimetry is poorly reproducible

- 18 tracers for which the ED was reported by two different teams
- The average relative difference among these tracers was 42%
- Only for 3 tracers the dose difference was smaller than 10%

^{11}C dosimetry has already been abandoned

-the Dutch experience

- University Hospital of Amsterdam abandoned both animal and human ^{11}C dosimetry for all tracers except those expected to enter routine clinical practice

- Adopted NIH protocol for ^{18}F tracers

Suggestions

- Abandon animal dosimetry for both ^{18}F and ^{11}C
- Perform ^{18}F human dosimetry after the tracer has been proven valid
- Abandon human ^{11}C dosimetry and use an average dose (5 µSv/MBq)