PET dosimetry - preclinical and human experience for clinical research

Nicholas Keat, William Hallett (speaker)

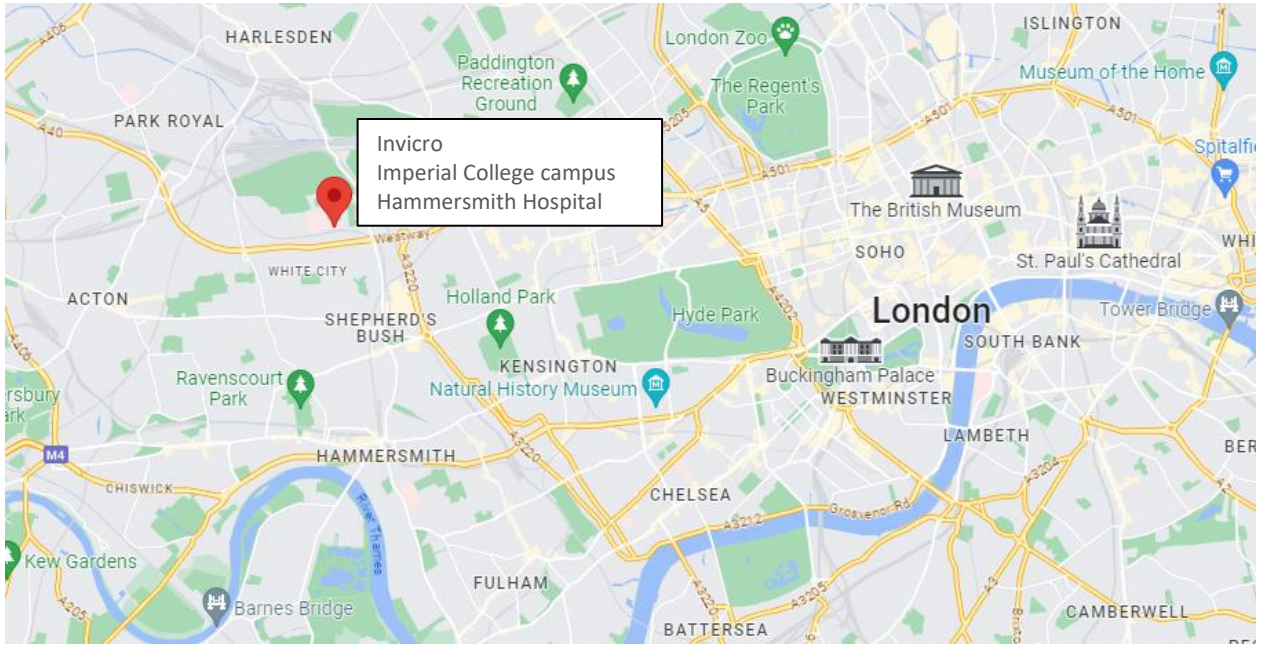
Medical physics
Invicro
London

Facility

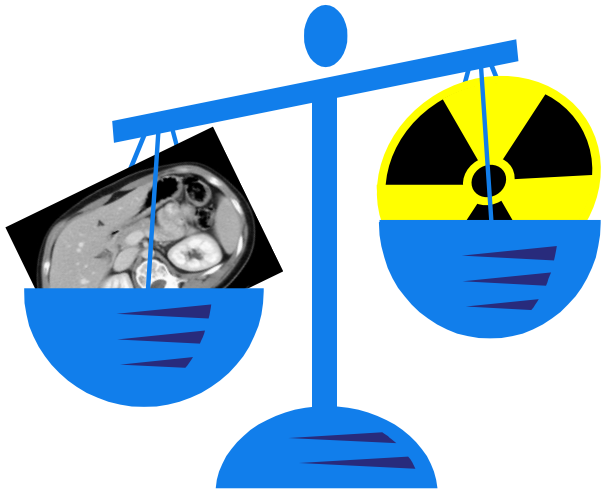
- 2 cyclotrons
- PET radiochemistry
- Biology
- Preclinical PET-CT
- Clinical PET-CT, MR, PET-MR

History

- 2006 GlaxoSmithKline
- 2011 Imanova – MRC/London University
- 2017 Invicro (US/UK)
  - Serving pharma and academia
  - PET ligand development
  - Mostly (not all) neuroreceptor studies



Why Radiation Dosimetry

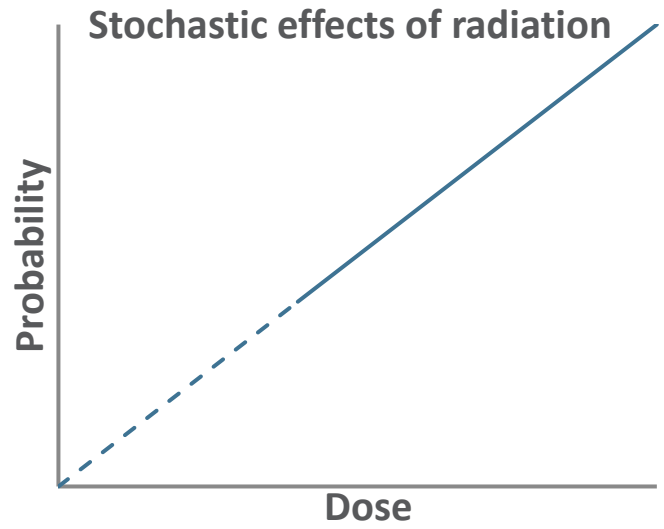


Justify and Optimise medical exposures

- EU Basic Safety Standards Directive 2013/59/Euratom 2013
- UK Ionising Radiation (Medical Exposure) Regulations 2017

Radiation dose to clinical subjects

- Probability of cancer, potential genetic effects
- Tissue effects (irrelevant for PET)
- Diagnostic Reference Levels for patients
- No dose limit

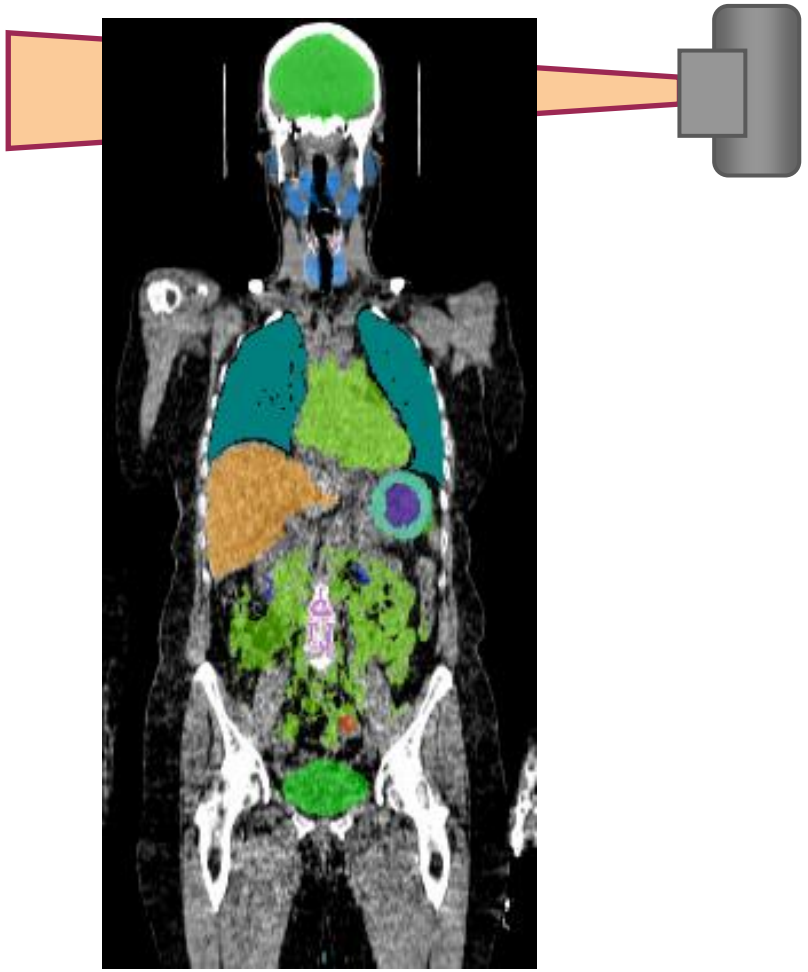


Ethical approval for research

- Equivalent background exposure
- Risk from radiation exposure
- Dose constraints and guidelines

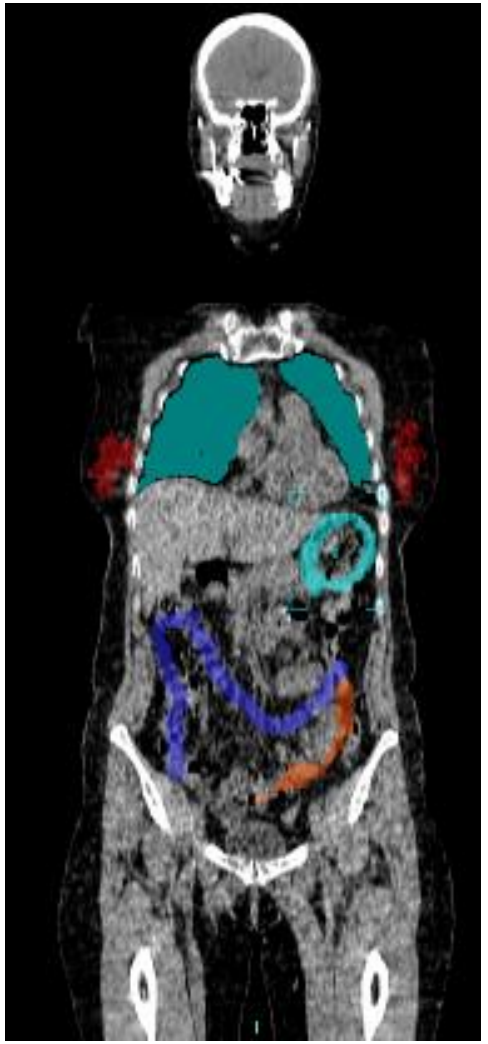
Radiation Dose

- Energy transferred by radiation to subject
- Absorbed dose (SI unit gray, Gy) = Joules per kg of tissue
- Diagnostic imaging -> mGy



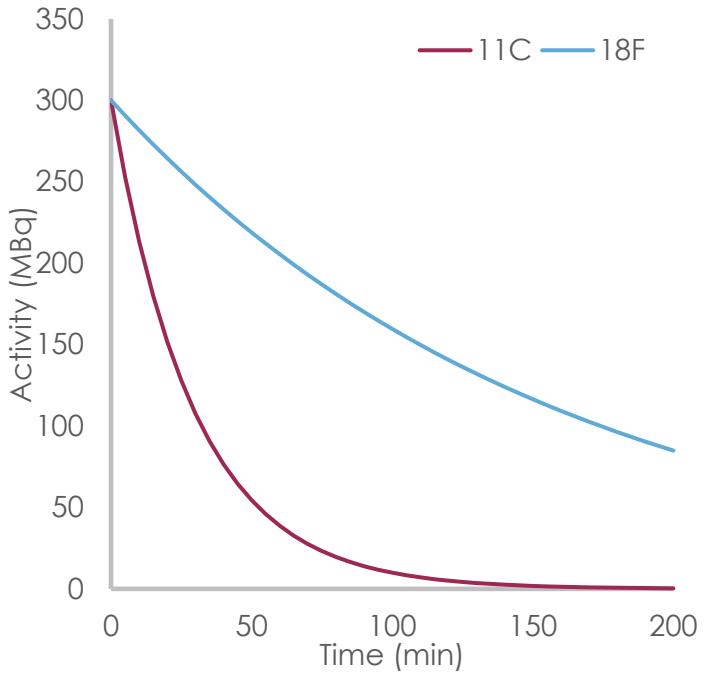
Radiation Risk

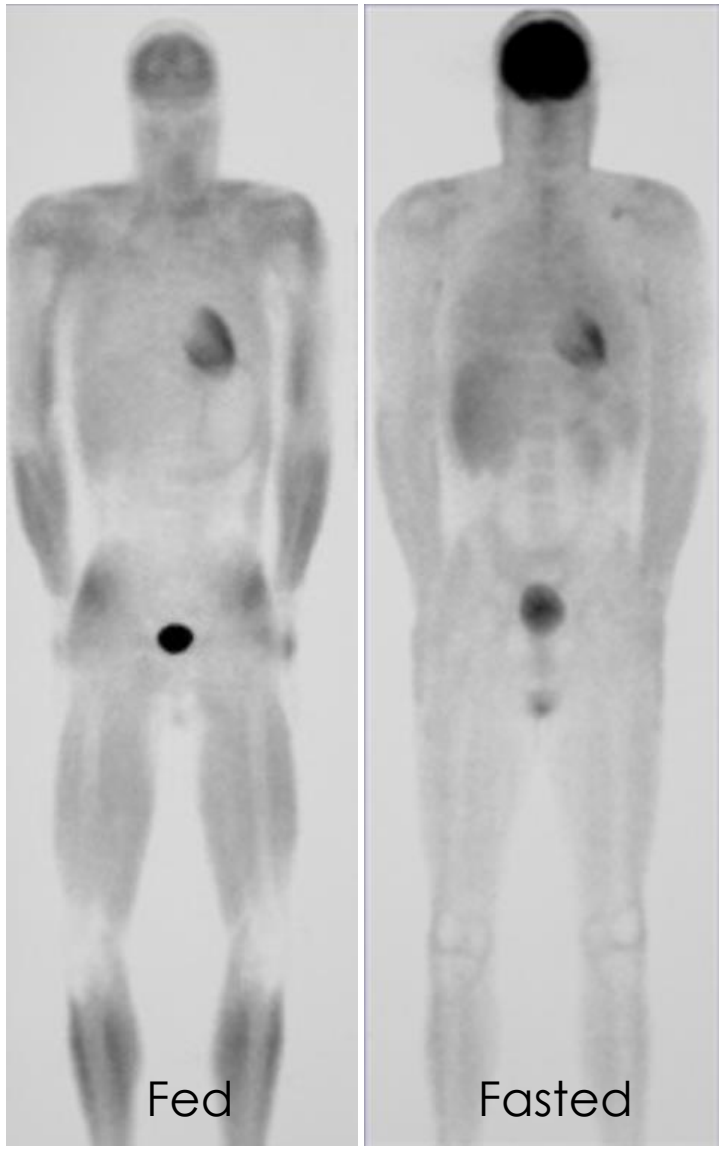
- Also depends on:
- Tissue / organs exposed
  - Radiation sensitivity of tissue (W_T)
  - Breast, bone marrow, colon, lung, stomach, (gonads) higher
- Radiation type
  - X rays, gamma rays, beta, positron (W_R=1)
- Effective dose ED = Sum over organs: Absorbed dose * W_R * W_T (sievert, Sv)
- UK background 2.3 mSv/year
- UK employee dose limit 20 mSv/year
- Lethal dose ~ 5 Sv
- Risk 1 mSv ~ 1/20000 (ICRP 103 - uncertain at low dose)



Factors affecting PET doses

- Activity, isotope, radioligand
- Biodistribution and excretion
  - subject: age, sex, weight, health, habitus etc

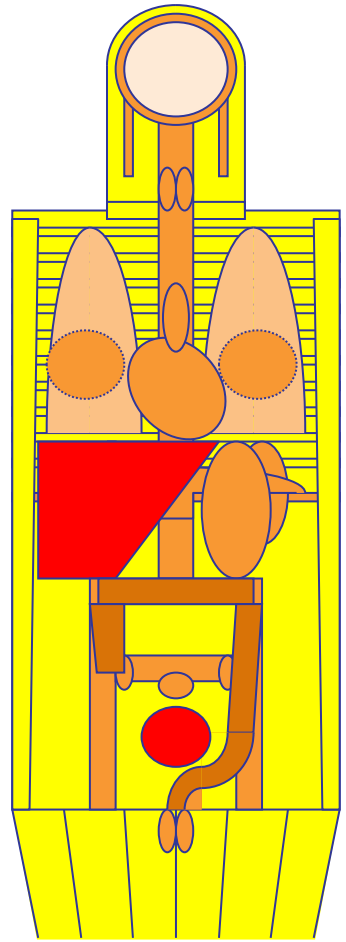




Standard Approach to PET dosimetry

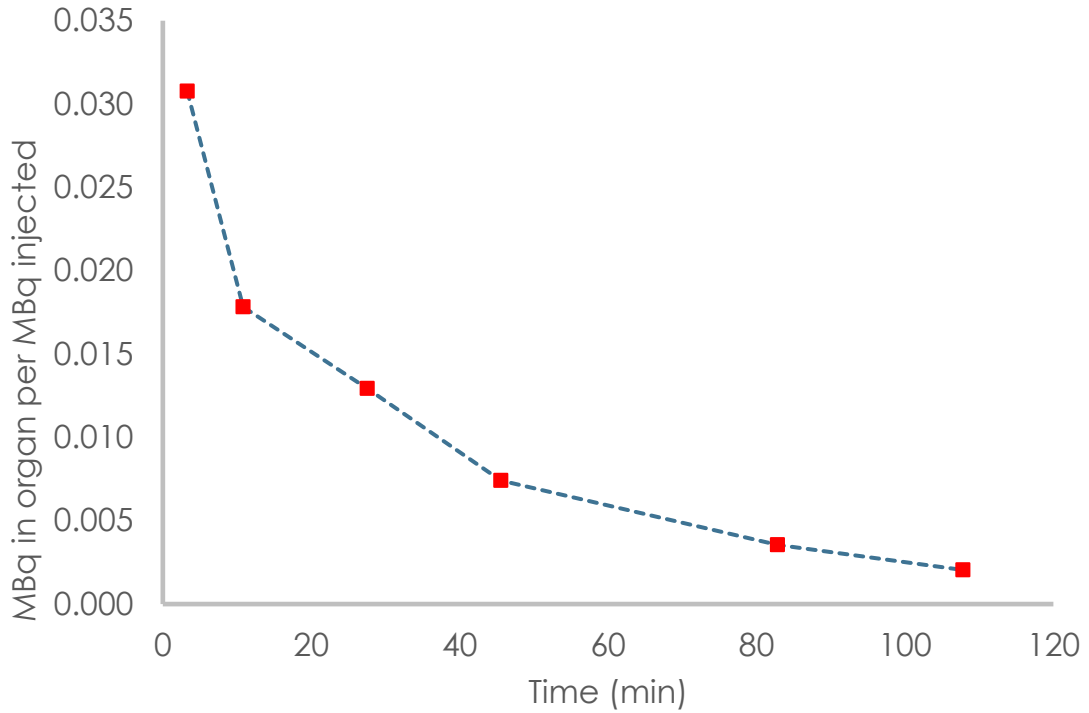
- Mathematical model
  - Simplified human ‘phantom’
  - Uniform body distribution too inaccurate
  - Organ activities from tissue samples (rodents) or imaging
- Compare medical exposures / PET drugs and estimate radiation risk
- Not accurate enough to plan or estimate individual doses
  - Organ doses are not measured!

Distribution	11C ED (µSv/MBq)	18F ED
Uniform	2.9	12.8
Model	6	20



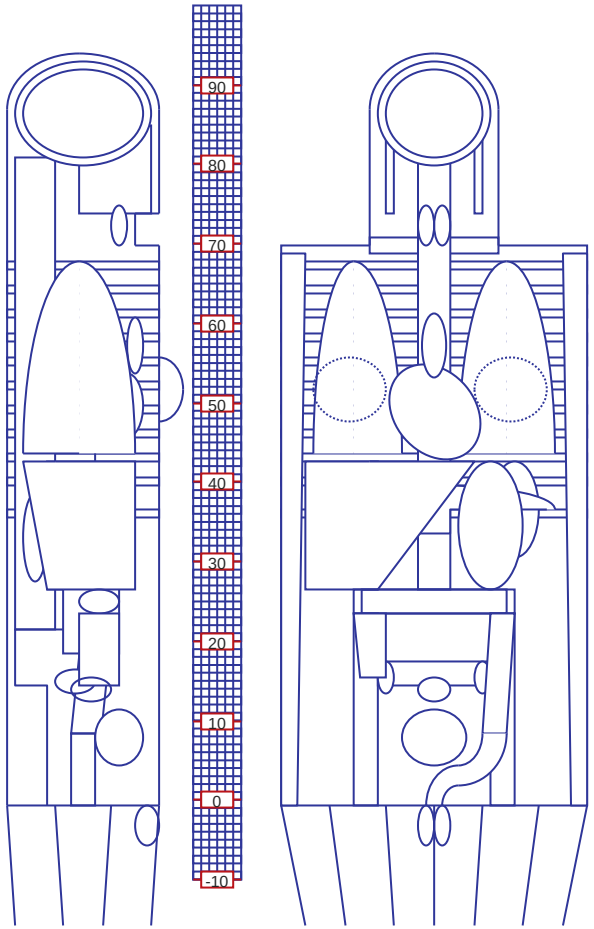
Time-integrated Activity Coefficients (TIACs)

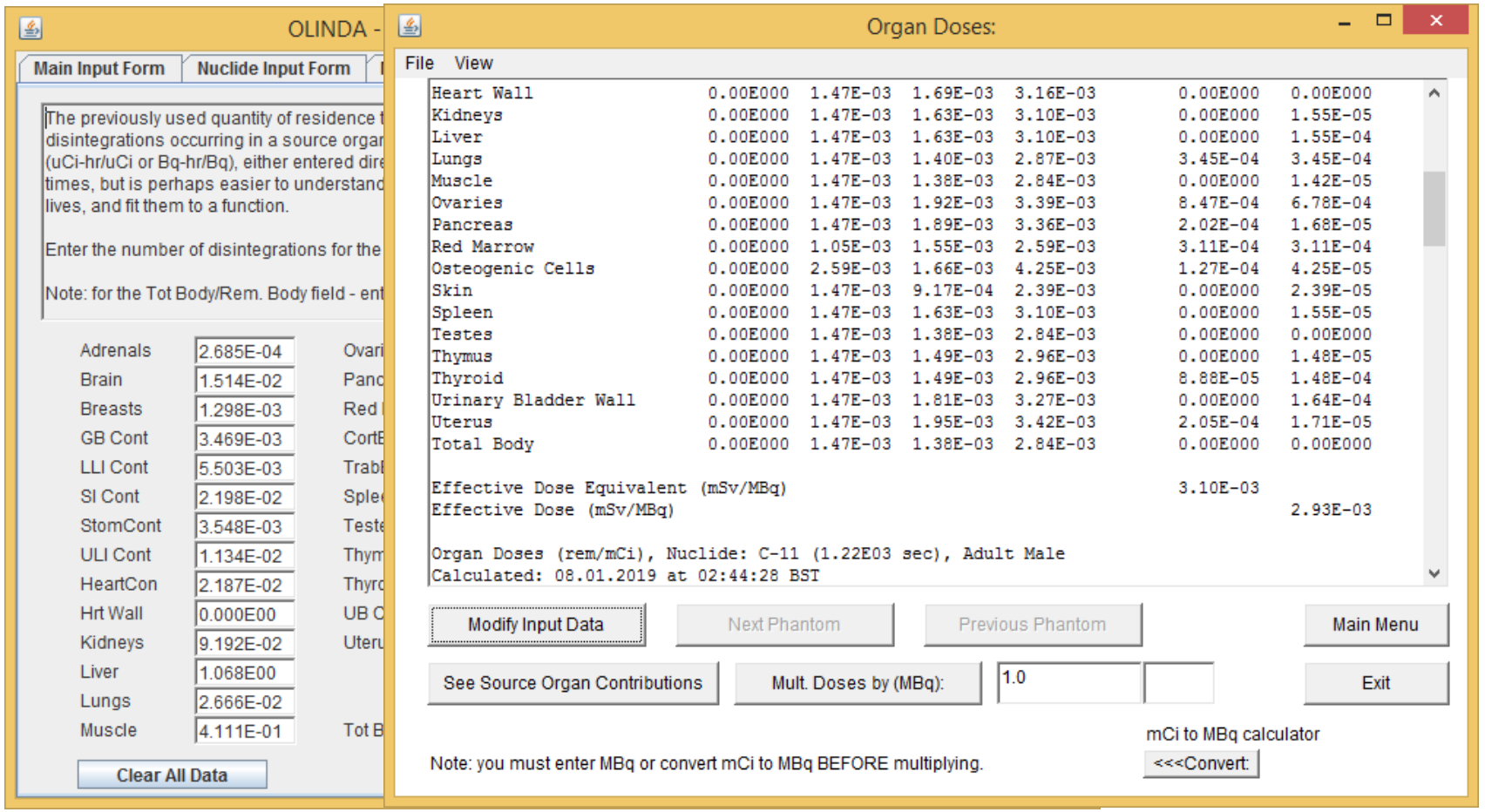
- Used in most dosimetry calculations
- Measure activity concentration at different time points
- Integrate specific activity concentration over time
- Multiply by standardised organ mass
- Specific total radioactive decays per organ ‘residence time’



Mathematical model OLINDA/EXM www.doseinfo-radar.com

- Inputs: Phantom type, isotope, TIACs in 'source' organs
- Outputs: Estimated dose to 'target' organs and effective doses



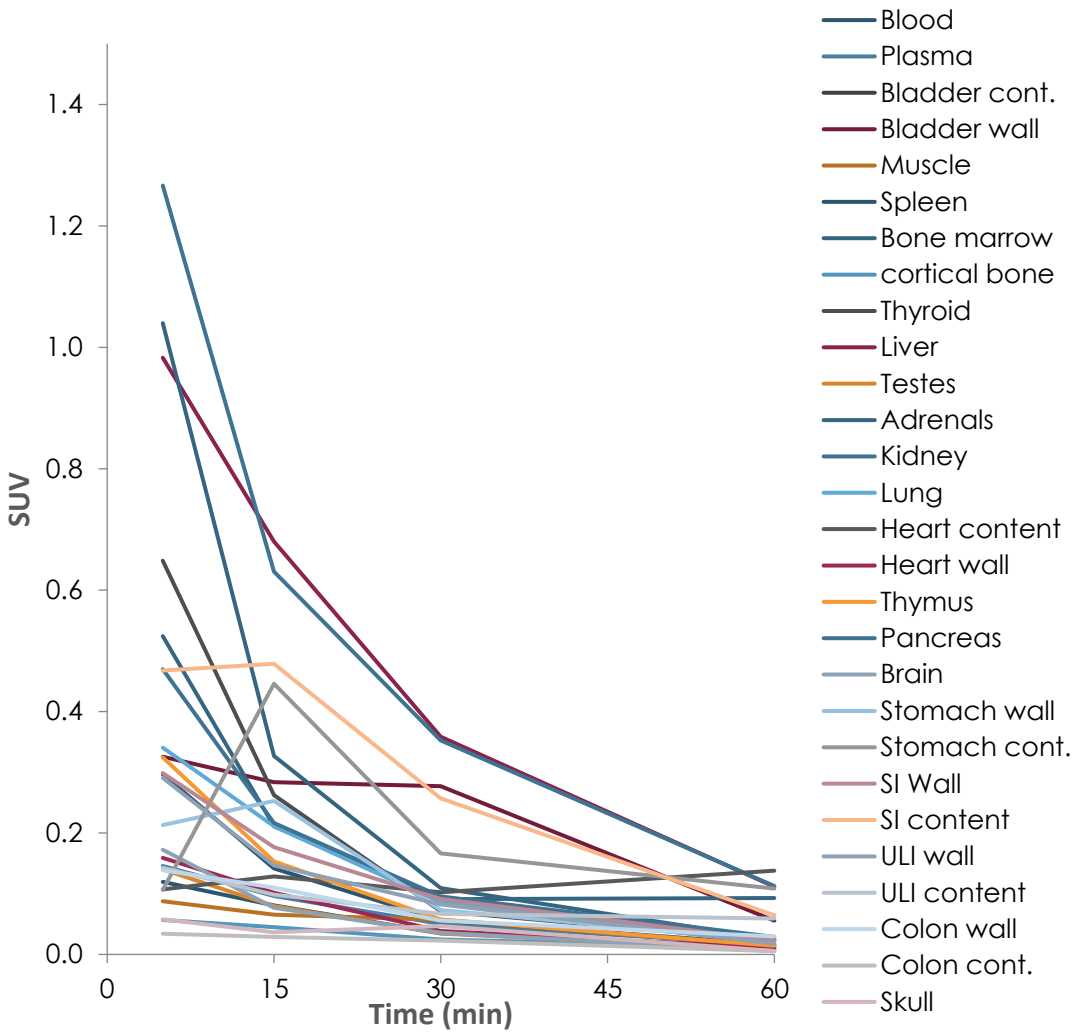


Preclinical PET dosimetry

- Give tracer to multiple subjects (IV)
- Sacrifice at set time points (e.g. 5, 15, 30, 60 mins)
- Harvest organs/tissue, weigh and count activity
- TIACs scale to human
- Input TIACs to OLINDA

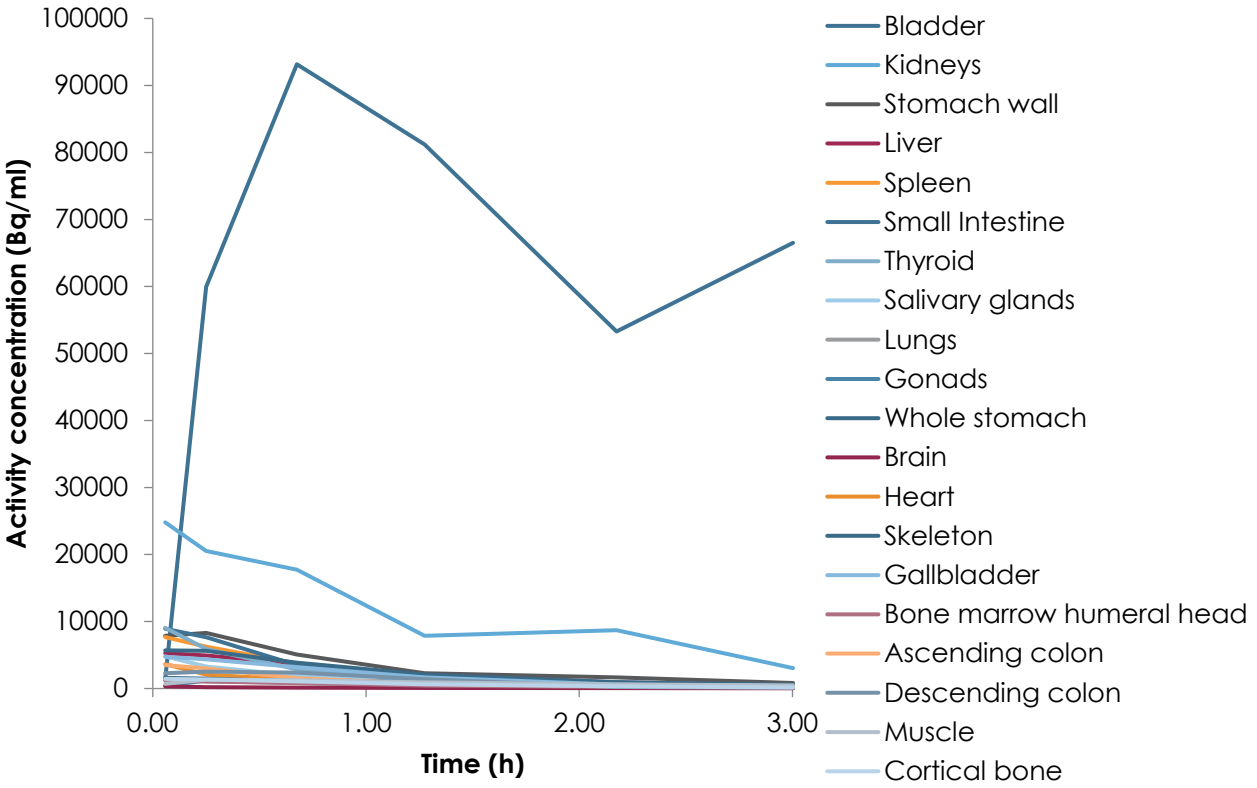
Figures below are decay corrected from injection to sample time, and adjusted for mass of animal

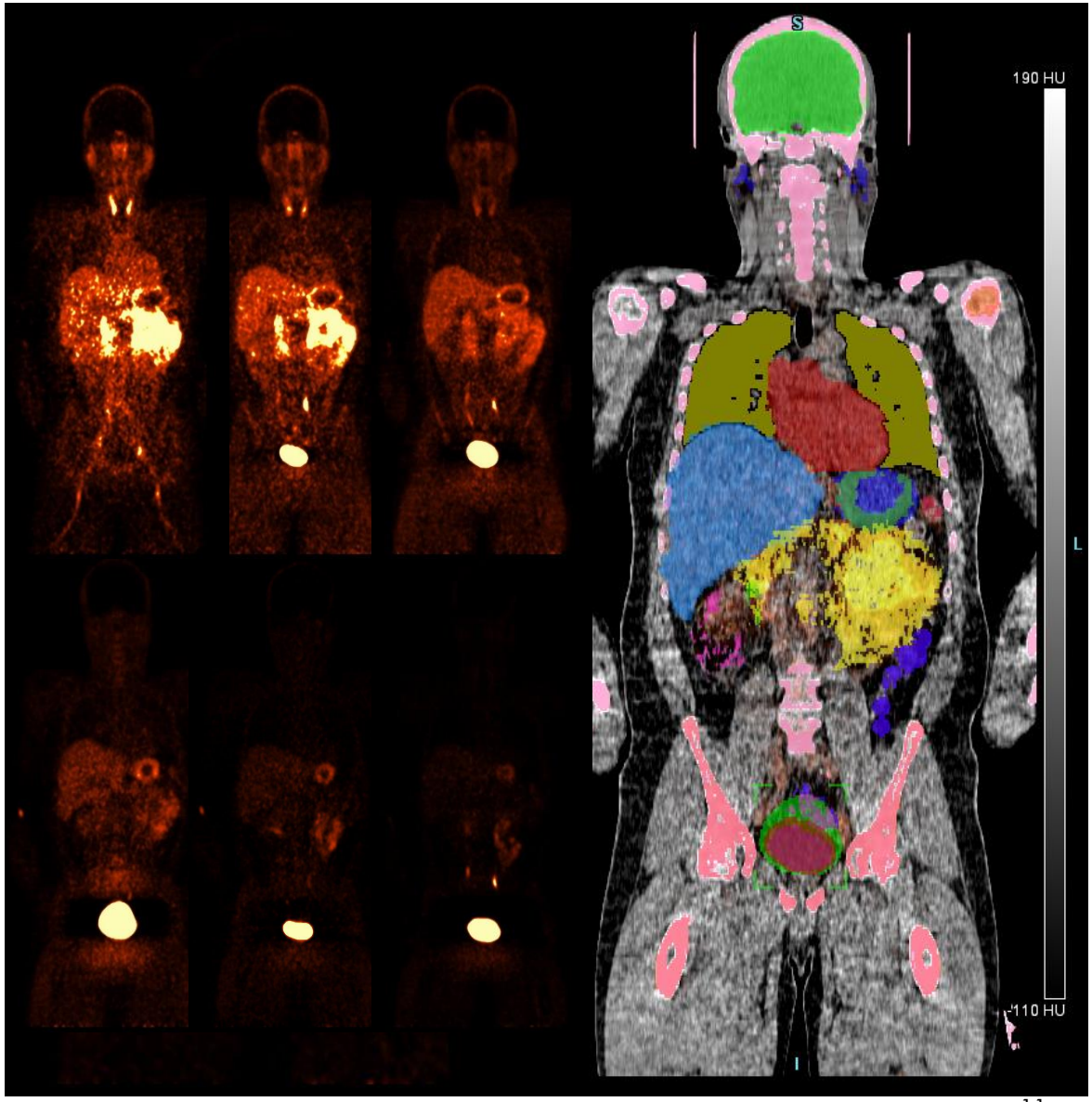
	5 min incubation				15 min incubation				30 min incubation				60 min incubation						
	n=1	n=2	n=3	mean	n=1	n=2	n=3	mean	n=1	n=2	n=3	mean	n=1	n=2	n=3	mean	Integral % ID (h)/g	Human organ mass (g)	Human scaled ID (h)
Animal mass (g)	373	356	377		374	386	352		396	371	350		415	387	364.7				
Blood	0.128	0.080	0.150	**0.120**	0.097	0.068	0.078	**0.081**	0.032	0.026	0.047	**0.035**	0.013	0.012	0.012	**0.013**	0.054	5000	0.0138
Plasma	0.158	0.095	0.184	**0.146**	0.111	0.086	0.092	**0.097**	0.044	0.041	0.066	**0.050**	0.018	0.014	0.016	**0.016**	0.069		
Bladder content	0.417	12.655	4.104	**5.726**	10.258	11.477	9.594	**10.443**	11.118	6.126	11.672	**9.638**	4.403	2.345	2.433	**3.060**	8.767	211	0.0942
Bladder wall	0.151	0.358	0.468	**0.326**	0.290	0.255	0.306	**0.284**	0.312	0.144	0.375	**0.277**	0.060	0.062	0.046	**0.056**	0.245	47.6	0.0006
Muscle	0.098	0.045	0.120	**0.088**	0.046	0.048	0.103	**0.066**	0.031	0.024	0.116	**0.057**	0.010	0.008	0.023	**0.014**	0.056	28000	0.0802
Spleen	0.355	0.237	0.298	**0.297**	0.141	0.128	0.156	**0.142**	0.055	0.048	0.066	**0.056**	0.018	0.014	0.017	**0.016**	0.100	183	0.0009
Red bone marrow	0.440	0.568	0.565	**0.524**	0.174	0.151	0.308	**0.211**	0.057	0.089	0.127	**0.091**	0.037	0.017	0.225	**0.093**	0.212	1120	0.0121
cortical bone	0.068	0.042	0.061	**0.057**	0.043	0.074	0.018	**0.045**	0.023	0.033	0.018	**0.025**	0.013	0.009	0.011	**0.011**	0.034	4000	0.0068
Thyroid	0.477	1.004	0.464	**0.648**	0.139	0.134	0.515	**0.262**	0.060	0.037	0.116	**0.071**	0.017	0.021	0.029	**0.022**	0.179	20.7	0.0002
Liver	1.109	0.679	1.160	**0.983**	0.648	0.579	0.813	**0.680**	0.340	0.243	0.494	**0.359**	0.113	0.115	0.108	**0.112**	0.482	1910	0.0468
Testes	0.180	0.094	0.147	**0.140**	0.085	0.067	0.087	**0.080**	0.030	0.022	0.052	**0.035**	0.008	0.008	0.006	**0.007**	0.053	39.1	0.0001
Adrenals	1.027	0.853	1.240	**1.040**	0.326	0.218	0.436	**0.327**	0.103	0.080	0.145	**0.109**	0.019	0.023	0.031	**0.025**	0.257	16.3	0.0002
Kidney	1.520	0.787	1.492	**1.266**	0.844	0.475	0.573	**0.631**	0.319	0.214	0.524	**0.352**	0.123	0.103	0.113	**0.113**	0.505	299	0.0077
Lung	0.368	0.256	0.398	**0.341**	0.220	0.172	0.242	**0.211**	0.091	0.059	0.108	**0.086**	0.030	0.021	0.023	**0.025**	0.137	1000	0.0070
Heart content	0.072	0.106	0.144	**0.107**	0.089	0.082	0.214	**0.129**	0.034	0.034	0.239	**0.102**	0.012	0.013	0.389	**0.138**	0.181	454	0.0042
Heart wall	0.175	0.123	0.180	**0.159**	0.102	0.095	0.109	**0.102**	0.037	0.029	0.050	**0.039**	0.012	0.009	0.011	**0.010**	0.063	316	0.0010
Thymus	0.377	0.237	0.360	**0.325**	0.134	0.139	0.186	**0.153**	0.052	0.045	0.076	**0.058**	0.017	0.013	0.013	**0.014**	0.105	20.9	0.0001
Pancreas	0.557	0.373	0.480	**0.470**	0.255	0.200	0.195	**0.217**	0.123	0.073	0.091	**0.096**	0.026	0.027	0.034	**0.029**	0.161	94.3	0.0008
Brain	0.209	0.113	0.195	**0.172**	0.075	0.072	0.083	**0.077**	0.042	0.026	0.040	**0.036**	0.008	0.008	0.001	**0.006**	0.055	1420	0.0040
Stomach wall	0.364	0.050	0.226	**0.213**	0.393	0.185	0.180	**0.253**	0.021	0.063	0.135	**0.073**	0.010	0.021	0.036	**0.022**	0.123	158	0.0010
Stomach content	0.064	0.012	0.244	**0.107**	0.862	0.282	0.194	**0.446**	0.075	0.087	0.338	**0.166**	0.058	0.037	0.231	**0.109**	0.249	260	0.0033
Small intestine wall	0.378	0.208	0.310	**0.299**	0.192	0.168	0.170	**0.177**	0.091	0.103	0.081	**0.091**	0.029	0.030	0.010	**0.023**	0.125	677	0.0043
Small intestine content	0.456	0.366	0.581	**0.468**	0.303	0.613	0.521	**0.479**	0.089	0.511	0.171	**0.257**	0.125	0.046	0.023	**0.065**	0.302	1100	0.0169
Upper large intestine wall	0.365	0.244	0.264	**0.291**	0.171	0.143	0.127	**0.147**	0.093	0.054	0.100	**0.083**	0.024	0.026	0.004	**0.018**	0.111	220	0.0012
Upper large intestine cont	0.240	0.062	0.126	**0.143**	0.112	0.096	0.088	**0.099**	0.084	0.046	0.070	**0.067**	0.026	0.025	0.127	**0.059**	0.107	232	0.0013
Colon wall	0.162	0.089	0.166	**0.139**	0.091	0.105	0.134	**0.110**	0.063	0.041	0.064	**0.056**	0.016	0.013	0.060	**0.030**	0.083	167	0.0007
Colon content	0.027	0.024	0.052	**0.034**	0.021	0.027	0.039	**0.029**	0.019	0.017	0.032	**0.023**	0.007	0.003	0.006	**0.005**	0.023	143	0.0002
skull	0.070	0.027	0.076	**0.058**	0.037	0.035	0.037	**0.037**	0.028	0.017	0.095	**0.047**	0.006	0.006	0.005	**0.006**	0.037	1000	0.0019
																	Total phantom mass	73700	0.2976
Mean animal mass (g)	375.1				Tail integral for decaying source			0.489									Total organ mass	48108.9	



Clinical PET dosimetry

- Give (IV) tracer to multiple subjects
- Scan repeatedly over 90 min / 4 hr period
- Outline organs with ROIs -> time activity curves
- Input TIACs to OLINDA





Our experience (Invicro London)

- 24 dosimetry studies since 2012

Species	n11C	Mean / range ED (µSv/MBq)	n18F	Mean / range ED (µSv/MBq)
Rat	9	5.5 / 4 - 7	9	25 / 18 - 35
Human	1	5.6	5	23 / 16 - 30

- 2 Ligands with rat and human dosimetry

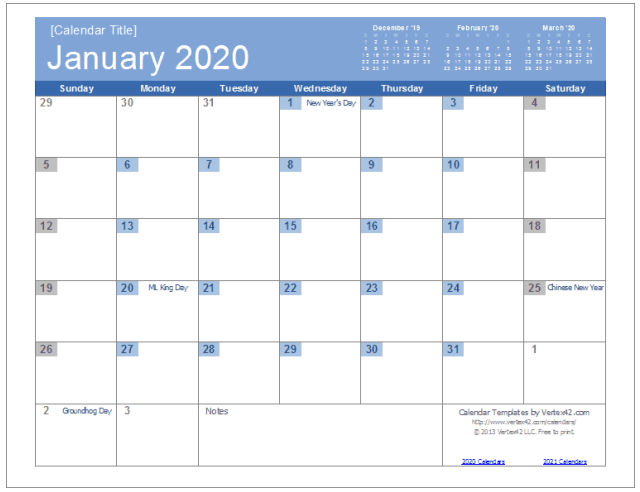
Species	AVB6 ED (µSv/MBq)	FPIA ED (µSv/MBq)
Rat	33.5	18.7
Human	21.7	15.9

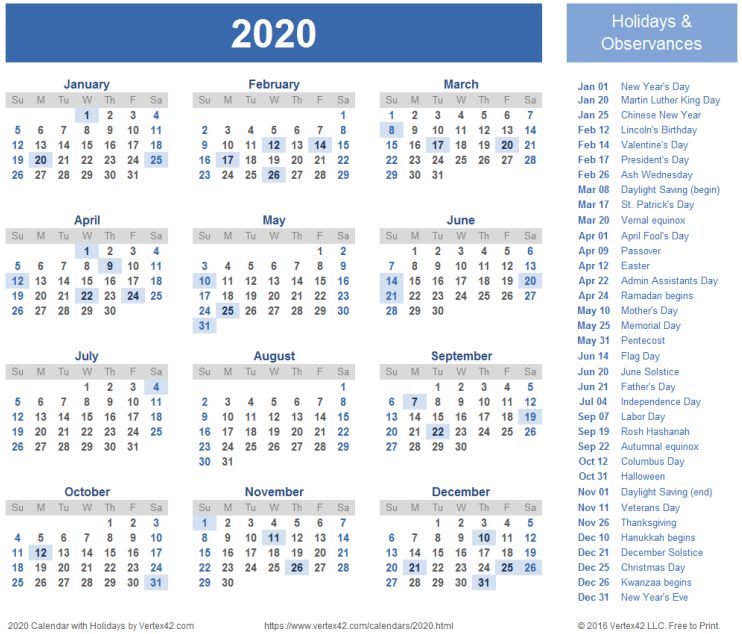
- 1 repeated rat study

Repeat number	AVB6 ED (µSv/MBq)
1	33.5
2	35.2

Study timelines

- Preclinical: 3 rats per time point, 4 time points
  - Occasional outlier (repeat if needed)
  - 3 scan days, few days data compilation, few days analysis
  - Quick turnaround: e.g 11C-Deprenyl
    - 29 Oct: “What is the fastest that we can do the dosimetry?”
    - 6, 8, 23 Nov: Experimental work
    - 26 - 28 Nov: Analysis and results
- Clinical: 4 subjects (2m, 2f), 8, 12, 24!
  - Long process…
    - Study development and funding – months
    - Preclinical dosimetry – 1-2 months
    - Ethics – 1-2 months
    - Recruitment, scanning – easier for healthy volunteers than patients - months
    - Analysis – 2+ weeks region drawing, analysis
    - 8-12 months+
  - Also far more expensive…



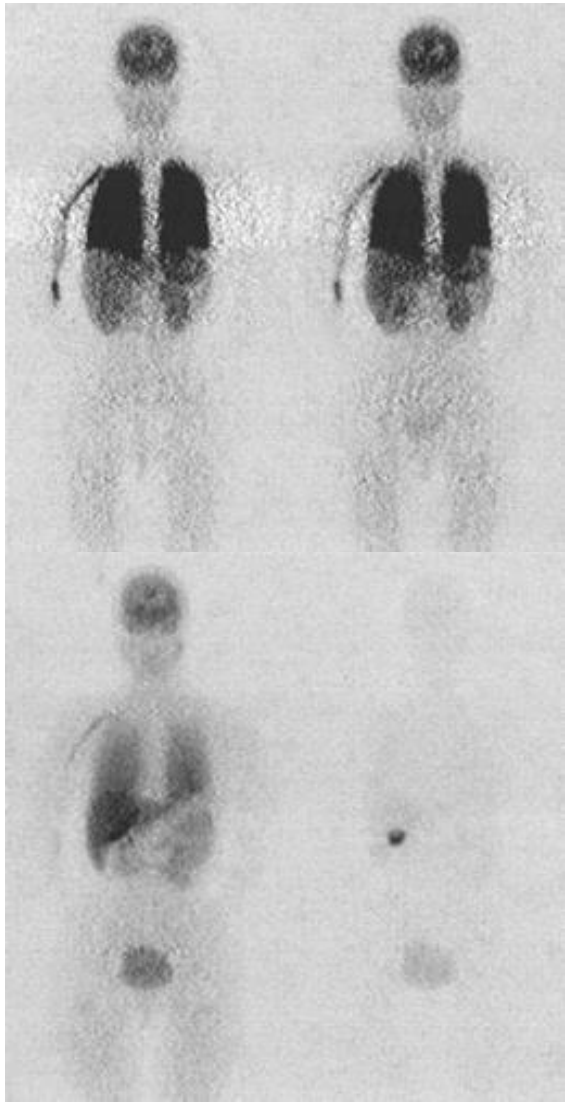


Tracers used at Invicro London

- In-house dosimetry: consistent techniques for 17 clinical ligands
- Another 55 ligands used clinically – dosimetry from other sources
  - Variable study quality/methodology
    - Often based on old data from PET only scanners
    - Different methodologies / models
    - Human, baboon, rhesus monkey, macaque, pig, dog, cat
  - Unknown details
    - Organs, bladder voiding, healthy vs patients etc

Species	n11C	Mean / range ED (µSv/MBq)	n18F	Mean / range ED (µSv/MBq)
Other	6	5.0 / 3.2-7.4	5	26 / 21-31
Rat	12	5.3 / 3.8-7.0	4	22 / 19-29
Human	15	5.7 / 3.9-7.7	29	24 / 12-33

- Are the differences due to methodology or metabolism?



Mixed results from pre-clinical to clinical translation

- Preclinical estimates of effective dose can be lower or higher than human
- Example: IMAFIB studies all performed at Invicro London

Tracer	Animal µSv/MBq		Human µSv/MBq
[11C]MRB	Baboon: 3.6		7.0
[11C]PHNO	Rat 5.1	Rhesus: 6.5	2.6
[18F]IMAFIB	Rat: 33.5	Repeat Rat: 35.2	21.7

- Methods seem to be repeatable, translation less so

Limitations of preclinical dosimetry

Rodents

- Differences in metabolism – more rapid in smaller species
- Lack of gall bladder in rat can give higher small intestine dose
- Renal excretion - need to translate to human voiding model
- Unreliable for human

Non-human primates

- Not generally performed in UK
- Still differences to human estimates

- Reduce animals used in research wherever possible (‘3Rs’)
- May indicate unusual kinetics / uptake
- Not reliable predictor for human dosimetry

Approaches to radiation protection: Europe vs US

Europe (including UK)

- ED typically < 10 mSv/year for healthy subjects [1]
- Can exceed 10 mSv/year for reduced life expectancy or elderly subjects
- More justification for younger healthy subjects
- Pre-clinical data acceptable if no human
- Dosimetry usually in healthy subjects, ED < 10mSv/year (including CT in PET-CT)

US

- ED / organ doses < 50 mSv/year (30mSv/year more radiosensitive organs) [2]
- Typically higher doses in US than Europe

[1] Derives from ICRP 62
[2] Derives from ICRP 26

UK – ARSAC approves use of radiopharmaceuticals

Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources

Administration of Radioactive Substances Advisory Committee

4.24 ARSAC expects that when an application for a research trial involving novel radiopharmaceuticals is submitted, estimates of effective dose will be based on the best information available at the time. Where such estimates are not possible from similar existing human studies, data from animal dosimetry studies, or where practicable from human studies involving extremely low radiation doses, should be submitted as part of the application. References to published works should be included on the application form and attached to the online portal with the application or, where this is not available; any unpublished data should be provided. For novel therapeutic radiopharmaceuticals, the protocol should allow for appropriate verification of treatment delivery where practicable.

4.25 More accurate information on dosimetry may be available once the trial commences. To help ARSAC in its task of reviewing future applications, such

information should be made available to the ARSAC Support Unit as soon as possible.

European guidance (draft)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2018
EMA/CHMP/SWP/686140/2018
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the non-clinical requirements for radiopharmaceuticals

Draft

5.3.1. Recommendations for Radiodiagnostics

In most cases microdose approach 1 of ICH M3(R2) will be used for radiodiagnostics since no pharmacological effect is intended and only a very small mass dose is administered after single administration.

5.3.1.1. Pharmacology

Radiodiagnostics are not intended to exert pharmacological activity, but evidence for the absence of pharmacological activity of the non-radioactive part should be provided. In this context, in vitro target/ receptor profiling is usually sufficient.

5.3.1.2. Pharmacokinetics

A biodistribution study including dosimetry should be performed with a single dose of the radiodiagnostic. Information on in vivo stability, distribution and elimination should be available to allow estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for distribution and persistence of the radiodiagnostic. If relevant, information should be provided on absorption and biotransformation.

5.3.1.3. Toxicology

According to microdose approach 1 outlined in ICH M3(R2), the results of an extended single dose toxicity study using the intended route of administration (usually i.v. route for radiodiagnostics), with toxicokinetic data should be available for the non-radioactive part.

When using the microdose approach 2, a repeat dose study for at least 7 days would be expected. A study of shorter duration may be considered on a case by case basis.

For both approaches a study in one species, usually rodent, can be generally considered sufficient.

Impact of dosimetry on research study design

Typical clinical research brain study at Invicro London

- Most studies need small number of subjects ~10-20

Isotope	CT dose (mSv)	PET dose (mSv)	PET-CT total (mSv)	Number of scans for 10 mSv
11C	0.3	0.006 * 300 = 1.8	2.1	4
18F	0.3	0.025 * 185 = 4.6	4.9	2

- Studies with a few 11C scans unlikely to reach 10 mSv

Alternatives

Assume default conservative effective dose

- Only a few outliers are higher (5%?)
  - ~ 8 µSv/MBq for 11C tracers
  - ~ 30 µSv/MBq for 18F tracers

Single whole body human scan to characterise uptake

- Potentially male and female, depending on study cohorts
- Representative?

Perform human dosimetry if use could exceed ~20 subjects

- May not be needed for seldom used tracers including many 11C