Small animal dosimetry
Dosimetric models vs. specific dosimetry

General dosimetric formalism

$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D)\, S(r_T \leftarrow r_S)$$

Absorbed dose calculation is a 3 step process:

- Quantitative imaging
- Time-integrated activity determination
- S factor calculation

Each step matters for the final result…

General dosimetric formalism

$$D\left(r_T, T_D\right) = \sum_{r_S} \tilde{A}\left(r_S, T_D\right) S\left(r_T \leftarrow r_S\right)$$

Absorbed dose calculation is a 3 step process:

- Quantitative imaging
- Time-integrated activity determination
- S factor calculation

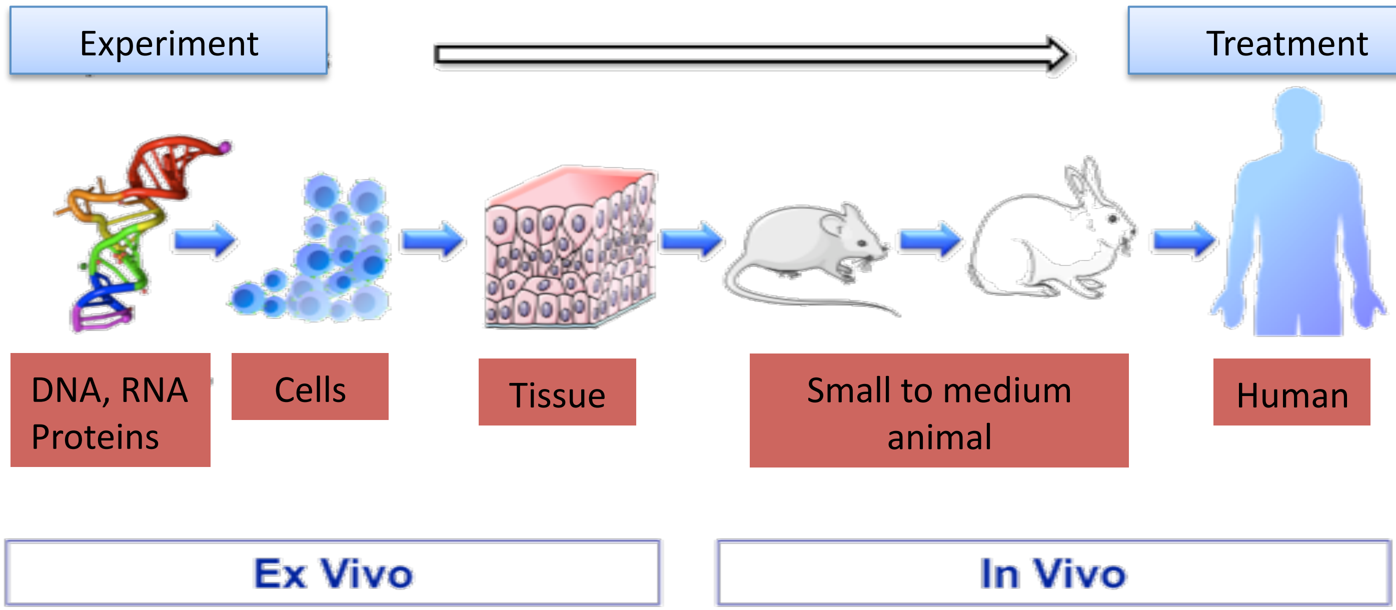
Optimizing one step means trying to optimize the others…

≠ possibilities

$\tilde{A}(r_S, T_D)$	$S(r_T \leftarrow r_S)$	$D(r_T, T_D)$
Group	model	model
Specific	Model ± adjusted	Model ± realistic
Specific	Specific	Specific

And this is true for preclinical or clinical experiments

For humans (patients) or (small) animals



Is dosimetry relevant for small animal experiments?

Testing a new radiopharmaceutical:

Assessing the biodistribution

Derive / extrapolate human biodistribution

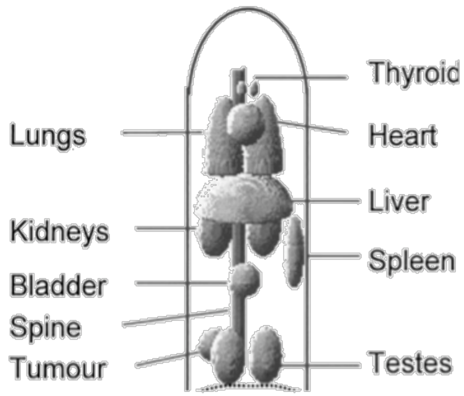
Dosimetry on human model

Animal dosimetry: to put in evidence/evaluate an effect

Efficacy/Toxicity

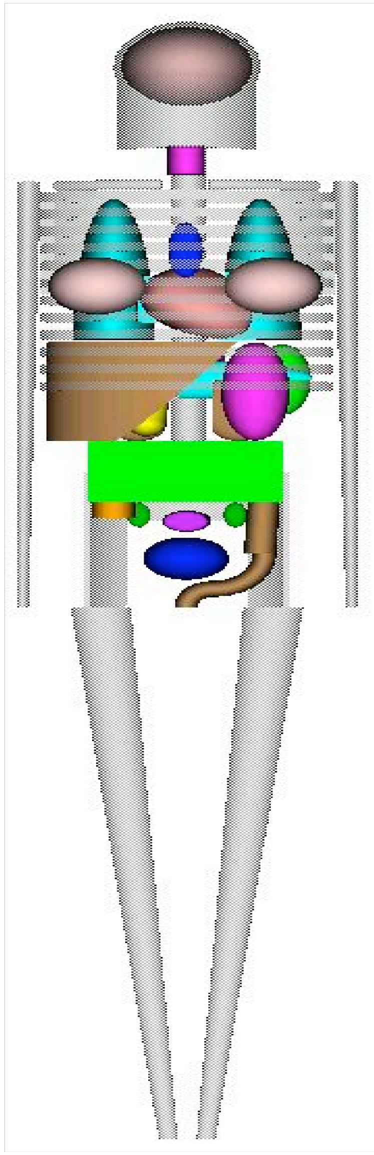
Specific vs. Model

Small animal



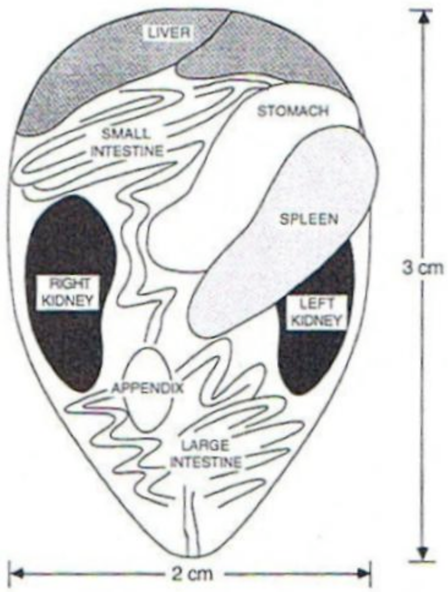
Hindorf et al.

Specific vs. Model



Small animal dosimetric models

Early attempts:
Hui TE, Fisher DR, Kuhn JA, et al.
A mouse model for calculating cross-organ beta doses from yttrium-90-labeled immunoconjugates.
Cancer. 1994;73(suppl): 951–957.

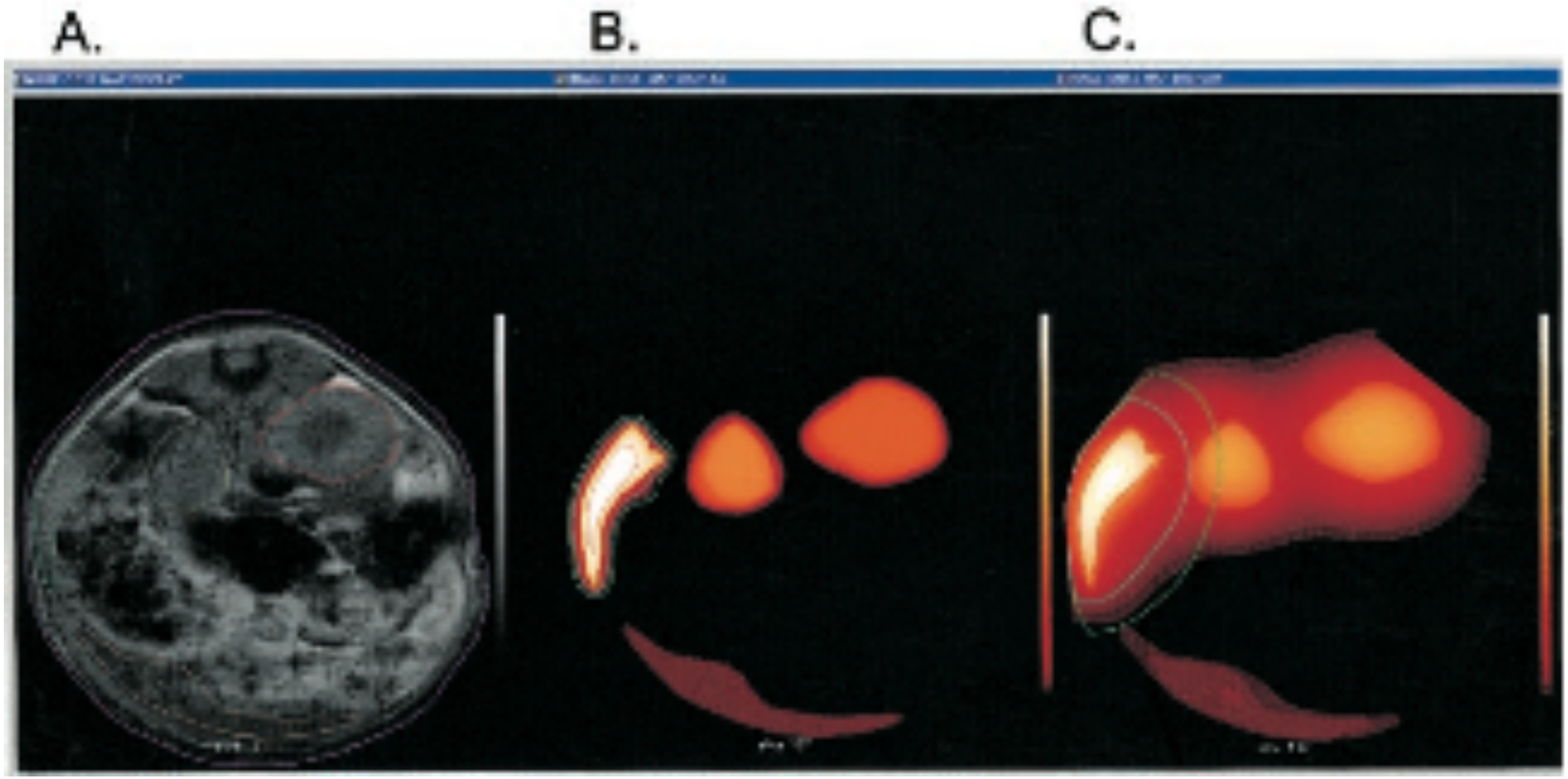


Yoriyaz H, Stabin M.
Electron and photon transport in a model of a 30 g mouse [abstract].
J Nucl Med. 1997;38:228P.

Muthuswamy MS, Roberson PL, Buchsbaum DJ.
A mouse bone marrow dosimetry model.
J Nucl Med. 1998;39:1243–1247.

Flynn AA, Green AJ, Pedley RB, Boxer GM, Boden R, Begent RH.
A mouse model for calculating the absorbed beta-particle dose from 131I- and 90Y-labeled immunoconjugates, including a method for dealing with heterogeneity in kidney and tumor.
Radiat Res. 2001;156:28–35.

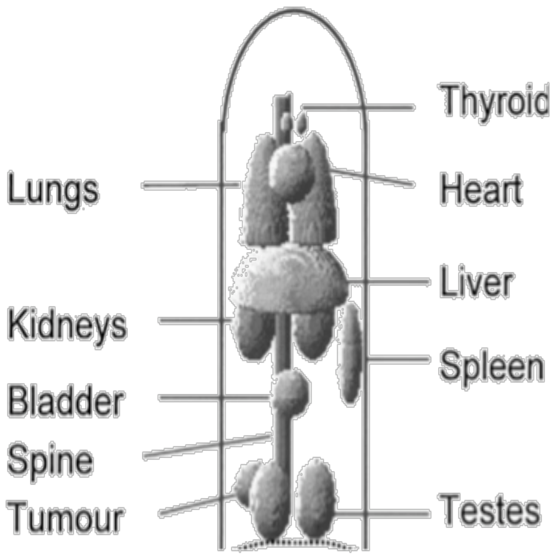
Small animal dosimetric models



Kolbert et al.

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 44 • No. 5 • May 2003

Small animal dosimetric models

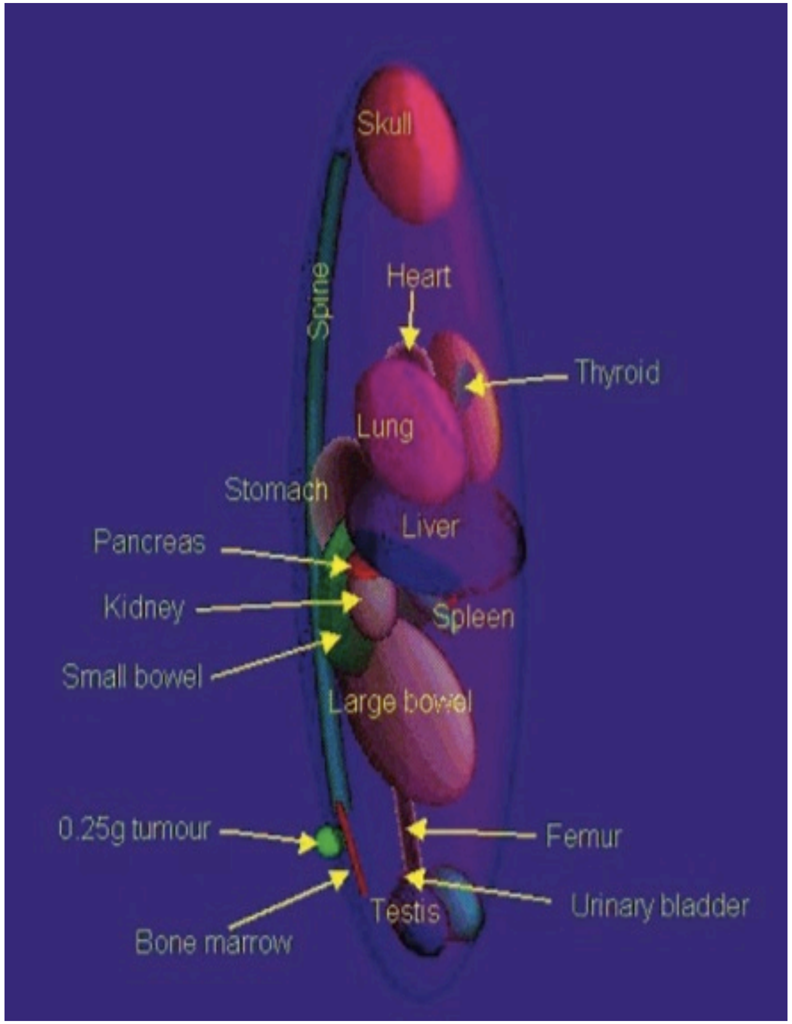


Hindorf et al.

« We conclude that the mass and the shape of organs and their locations relative to each other have considerable effects on mouse dosimetry »

Hindorf et al 2004, J Nucl Med

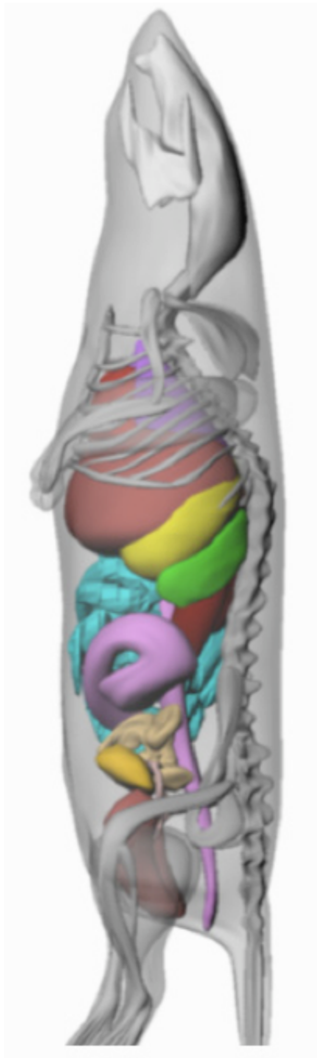
Small animal dosimetric models



Konijnenberg 2004

More recently: voxel-based models

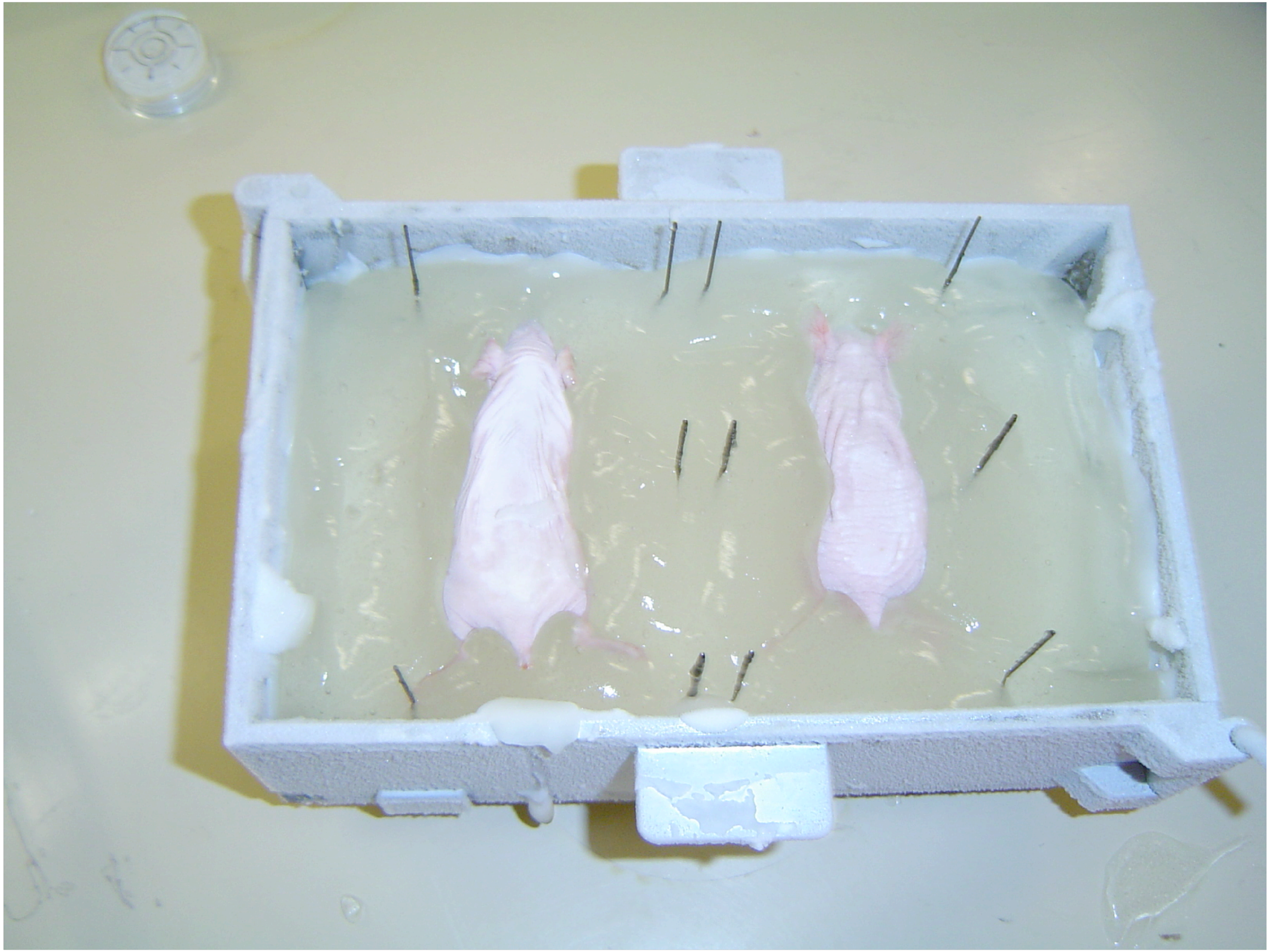
Stabin 2006



Larsson 2007

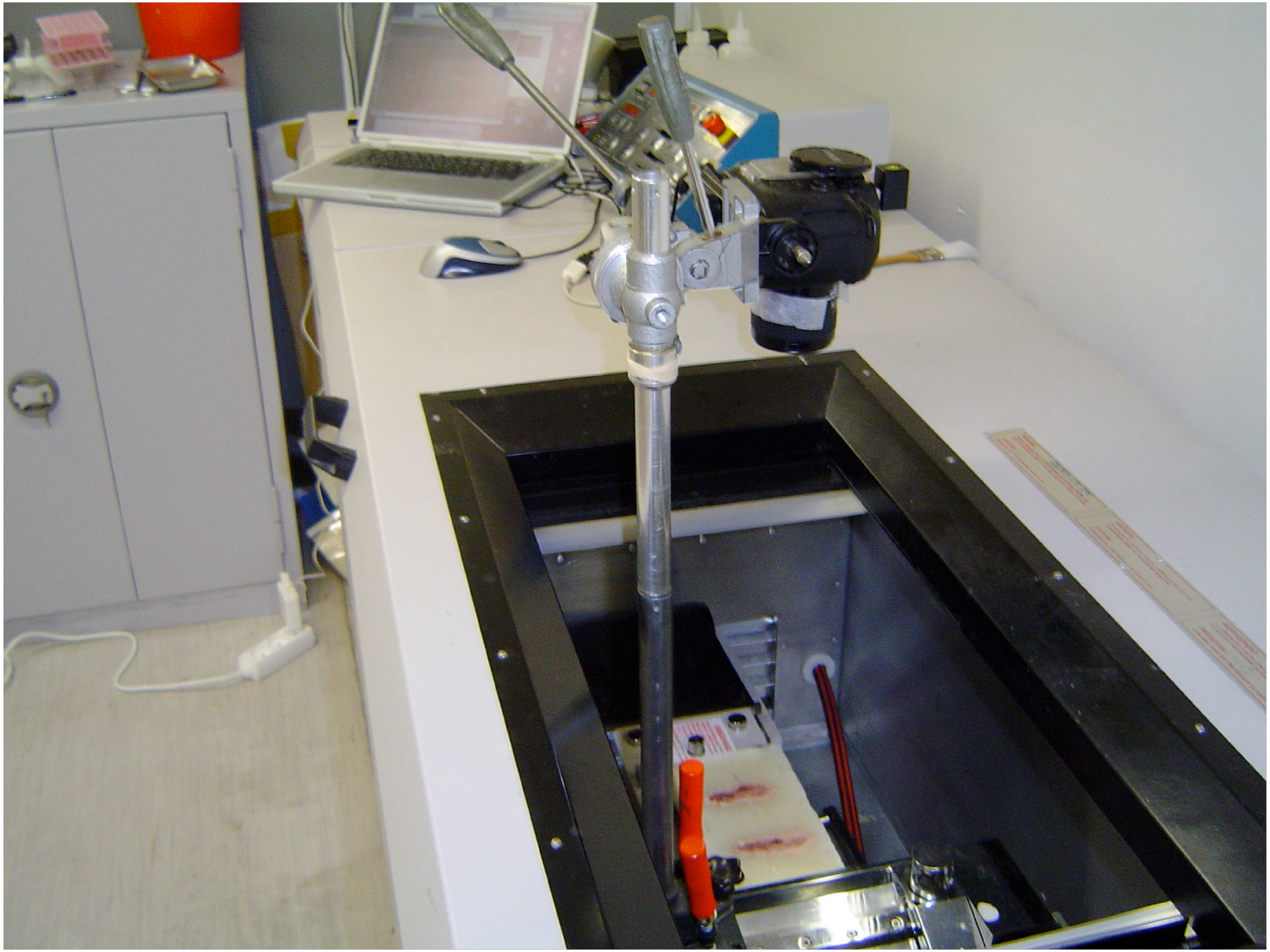
Bitar 2007

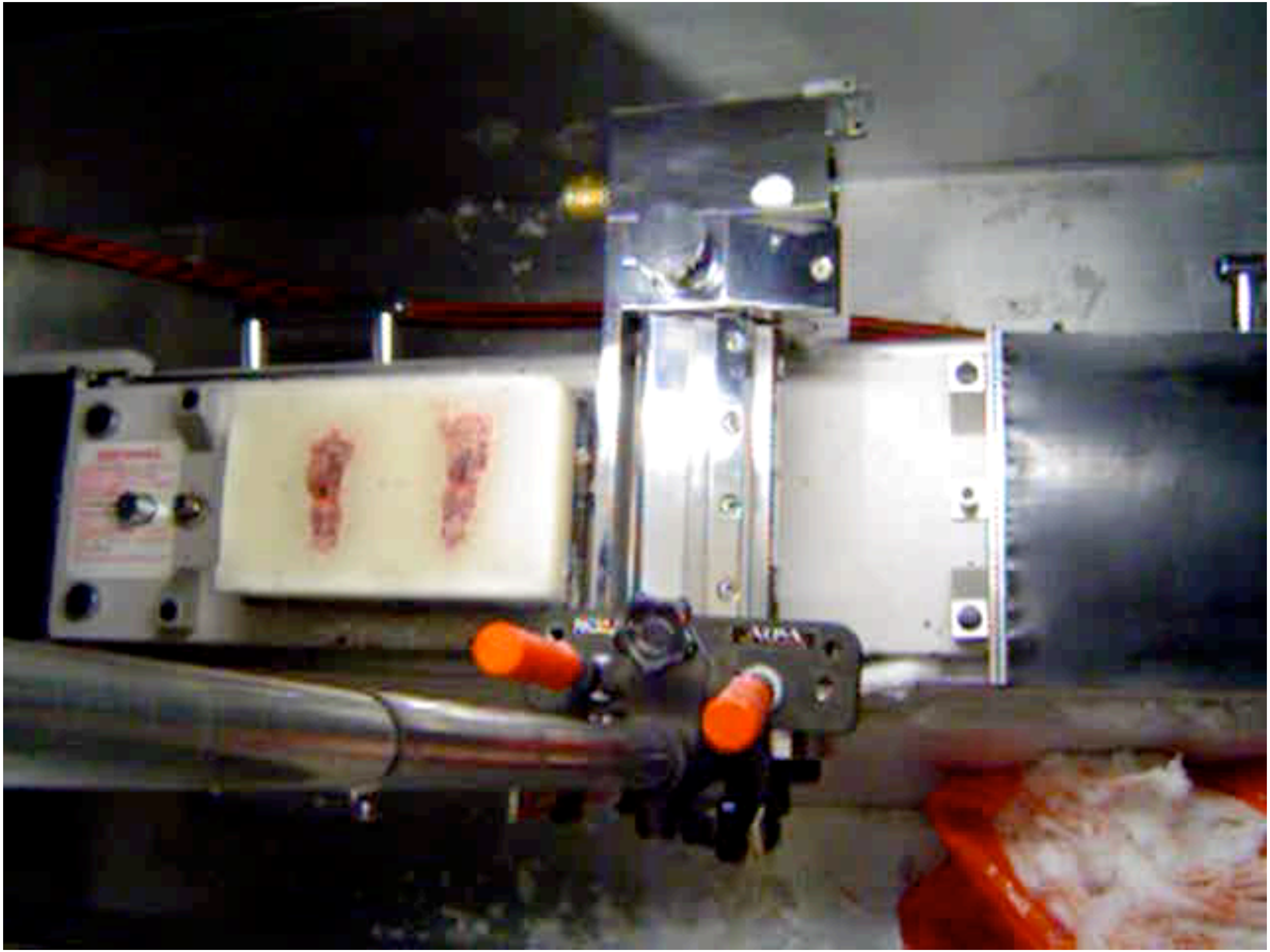
Experimental set-up

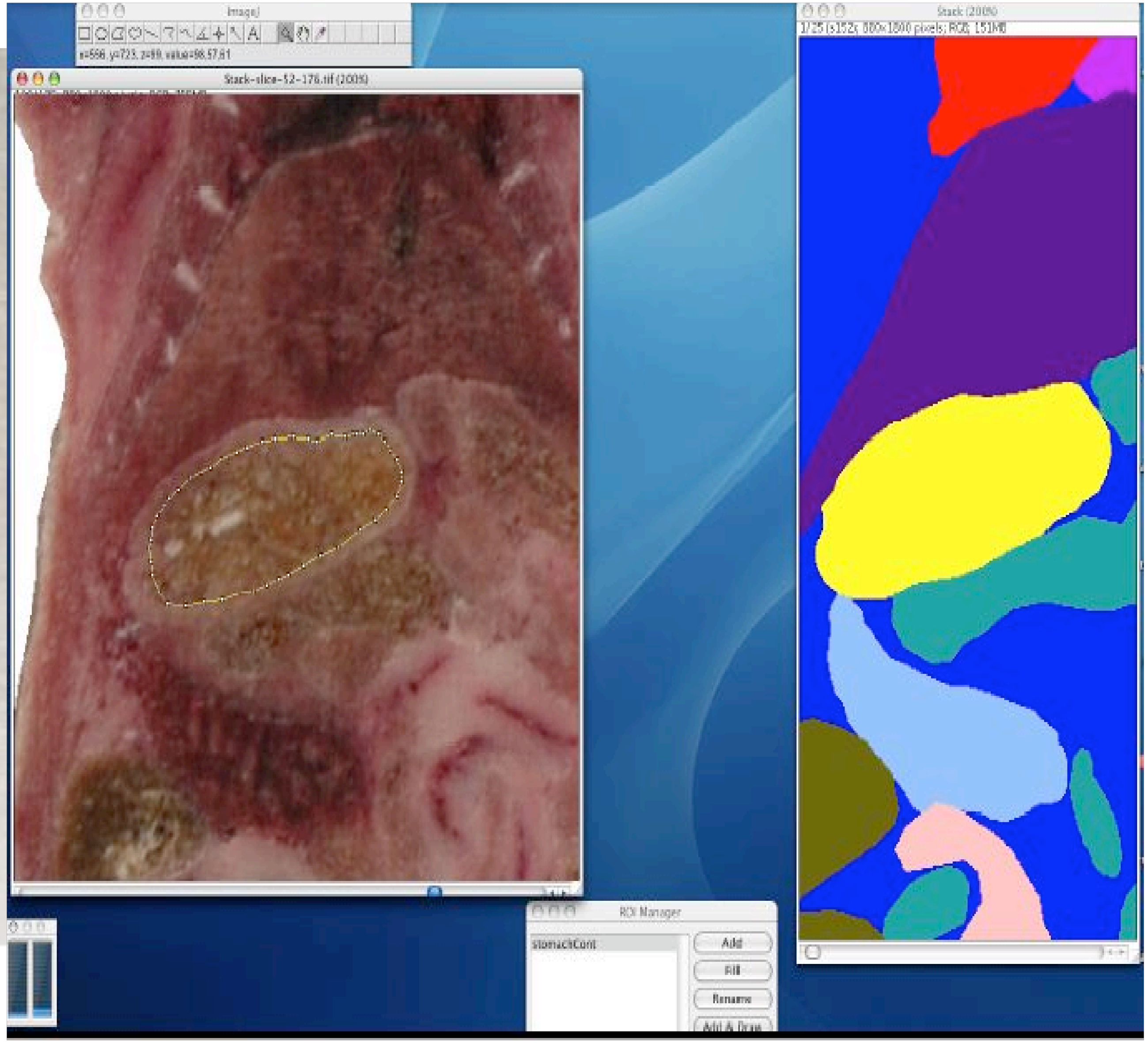


Experimental set-up

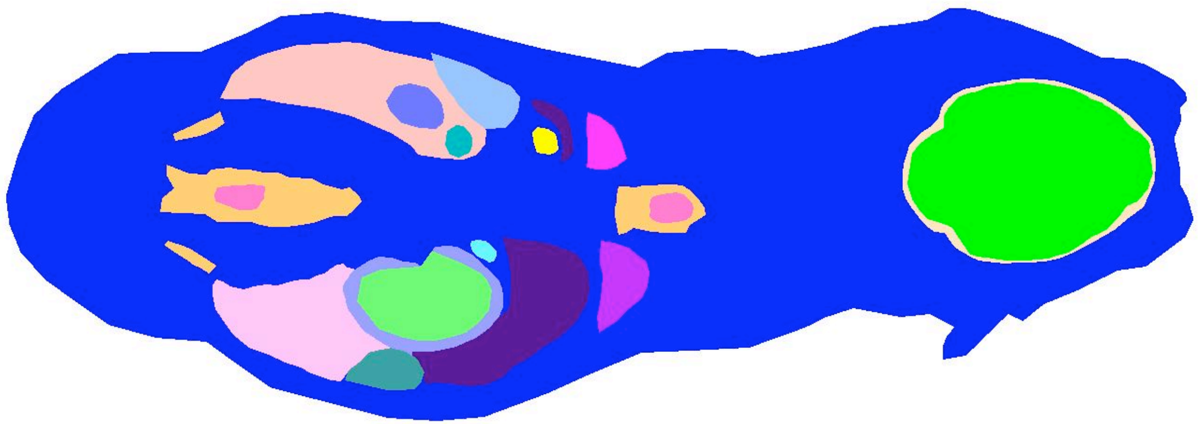
Experimental set-up



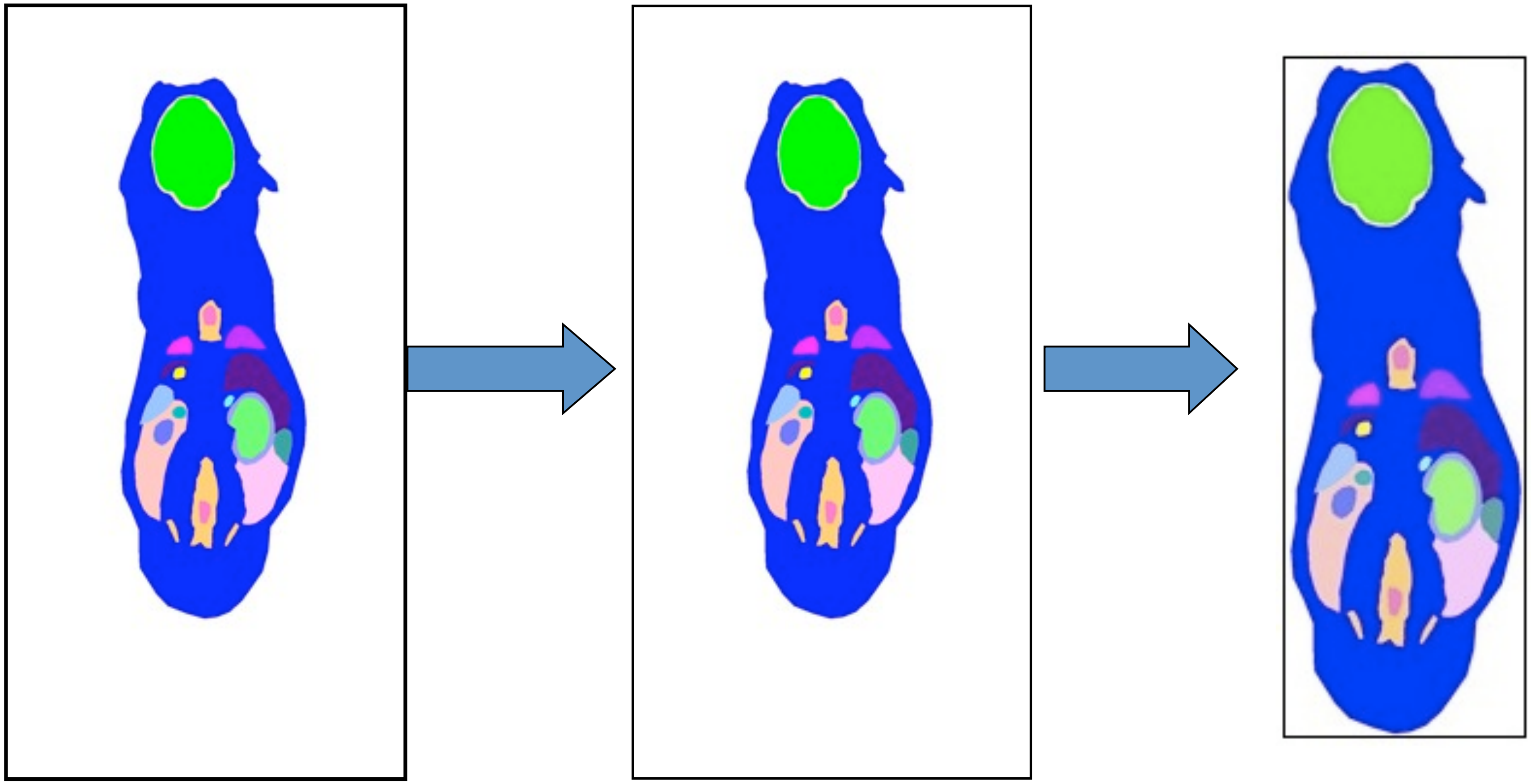



ImageJ
Stack-slice-52-176.tif (200%)
ROI Manager
stomachCont
Add
Fill
Rename
Stack (200%)

Segmenting images



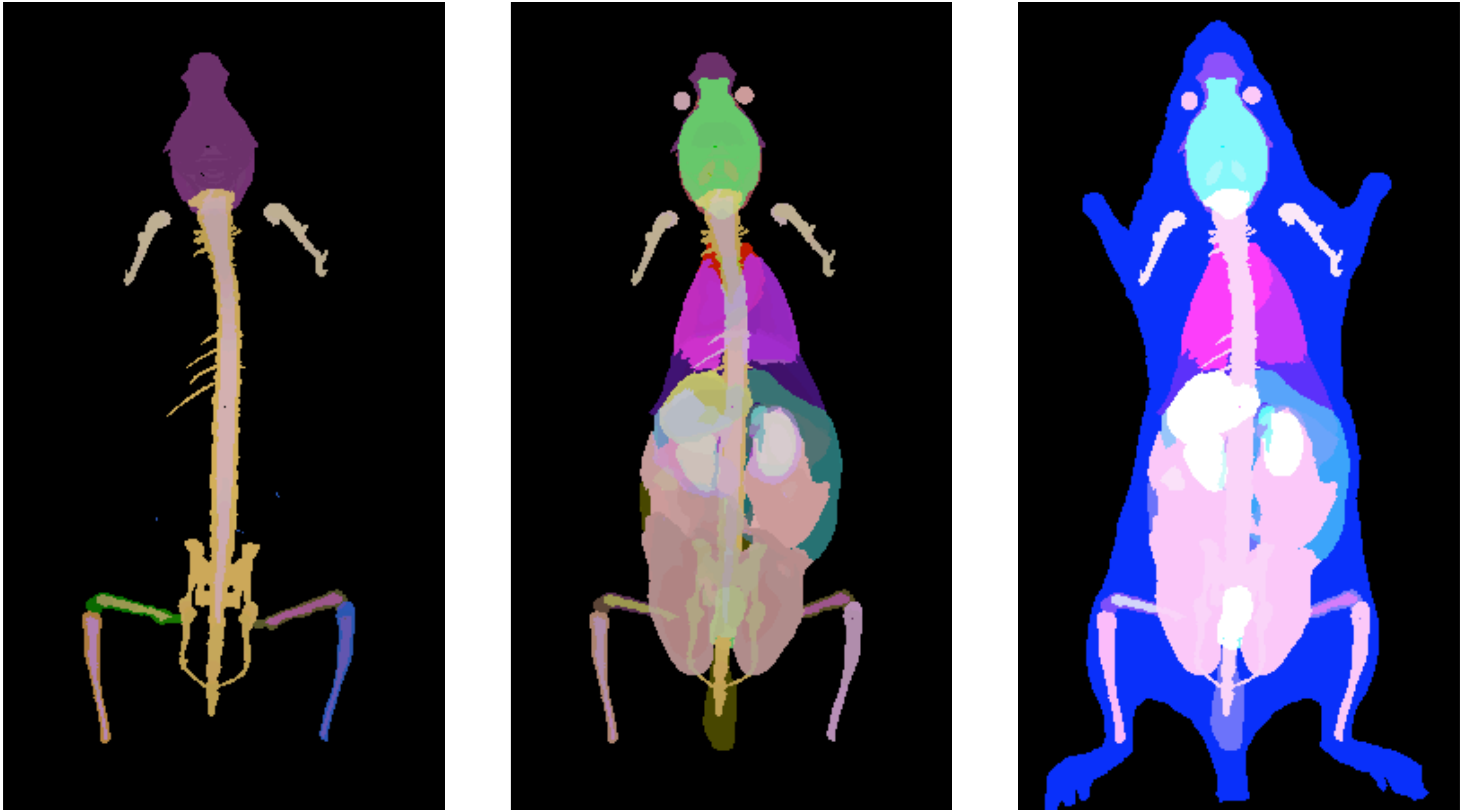
Reducing the number of voxels



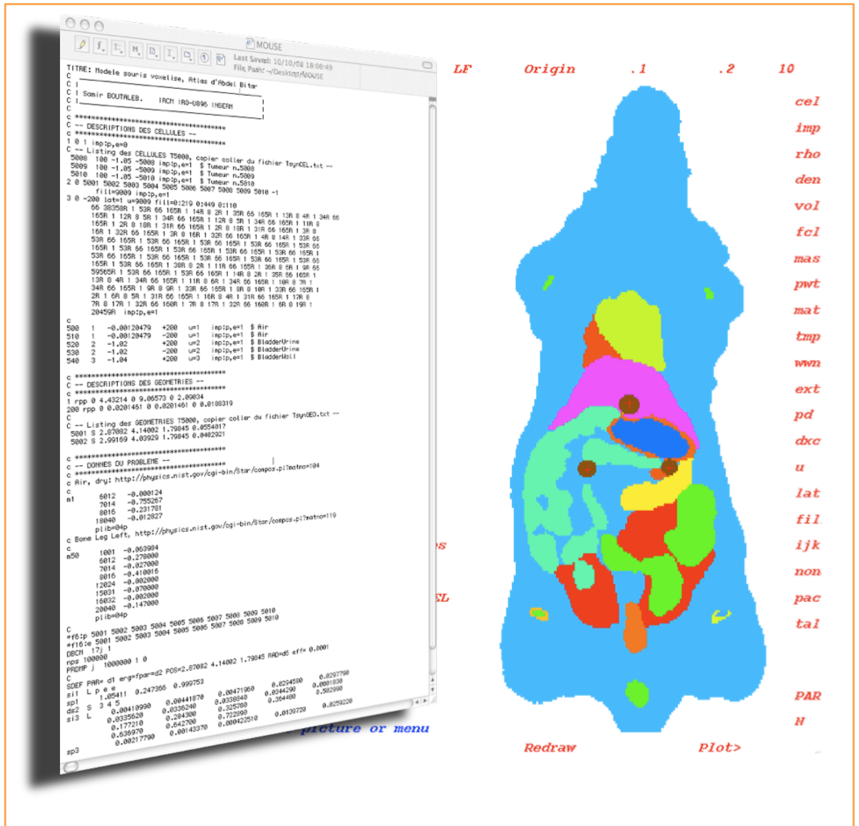
221x880x1800 (350x10^6 voxels) 111x220x450 (11x10^6 voxels) 104x317 (5.5x10^6 voxels)

Organe		Symbole	Densité ($g.cm^{-3}$)	Masse (g)
Nom français	Nom anglais			
Vessie (contenu)	Bladder (content)	BdC	1.02	0.0144
Vessie (paroi)	Bladder (Wall)	BdW	1.04	0.0102
Vessie (contenue+paroi)	Bladder (content+Wall)	Bdr	1.02/1.04	0.0245
Os patte gauche	Bone limb Left	BoL	1.85	0.0726
Os patte droit	Bone limb Right	BoR	1.85	0.0695
Cerveau	Brain	Brn	1.04	0.5159
Carcasse	Carcass	Car	1.04	20.8605
Côlon	Colon	Col	1.03	1.2395
Graisse	Fat	Fat	0.95	1.8587
Coeur	Heart (blood filled)	Hrt	1.06	0.2816
Rein gauche (Cortex)	Left Kidney (Cortex)	KLC	1.05	0.0834
Rein gauche (Medulla)	Left Kidney (Medulla)	KLM	1.05	0.0979
Rein gauche (Cortex+Medulla)	Left Kidney (Cortex+Medulla)	KdL	1.05	0.1813
Rein droit (Cortex)	Right Kidney (Cortex)	KRC	1.05	0.0845
Rein droit (Medulla)	Right Kidney (Medulla)	KRM	1.05	0.1110
Rein droit (Cortex+Medulla)	Right Kidney (Cortex+Medulla)	KdR	1.05	0.1955
Foie	Liver	Lvr	1.06	1.8305
Poumon gauche	Left Lung	LgL	0.26	0.0409
Poumon droit	Right Lung	LgR	0.26	0.0819
Poumons (gauche+droit)	Lungs (Left+Right)	Lgs	0.26	0.1228
Moelle osseuse (patte gauche)	Left limb Marrow	MrL	1.03	0.0166
Moelle osseuse (patte droite)	Right limb Marrow	MrR	1.03	0.0168
Ovaire gauche	Left Ovary	OvL	1.05	0.0093
Ovaire droit	Right Ovary	OvR	1.05	0.0088
Pancréas	Pancreas	Pnc	1.04	0.0895
Crâne	Skull	Skl	1.85	0.2965
Intestin grêle	Small Intestine	SIn	1.03	1.6874
Moelle spinale	Spinal Cord	SpC	1.04	0.1121
Rate	Spleen	Spn	1.06	0.2164
Estomac (paroi)	Stomach (Wall)	StW	1.05	0.1616
Estomac (contenu)	Stomach (Contents)	SCo	1.05	0.2761
Estomac (paroi+contenu)	Stomach (Wall+Contents)	Stc	1.05	0.4378
Surrénal gauche	Left Suprarenal	SRL	1.04	0.0056
Surrénal droit	Right Suprarenal	SRR	1.04	0.0050
Thyroïde	Thyroid	Tyd	1.05	0.0052
Utérus	Uterus	Uts	1.05	0.0455
Vertèbres	Vertebrae	Vtb	1.85	0.6020

Result: mouse dataset



Calculation step

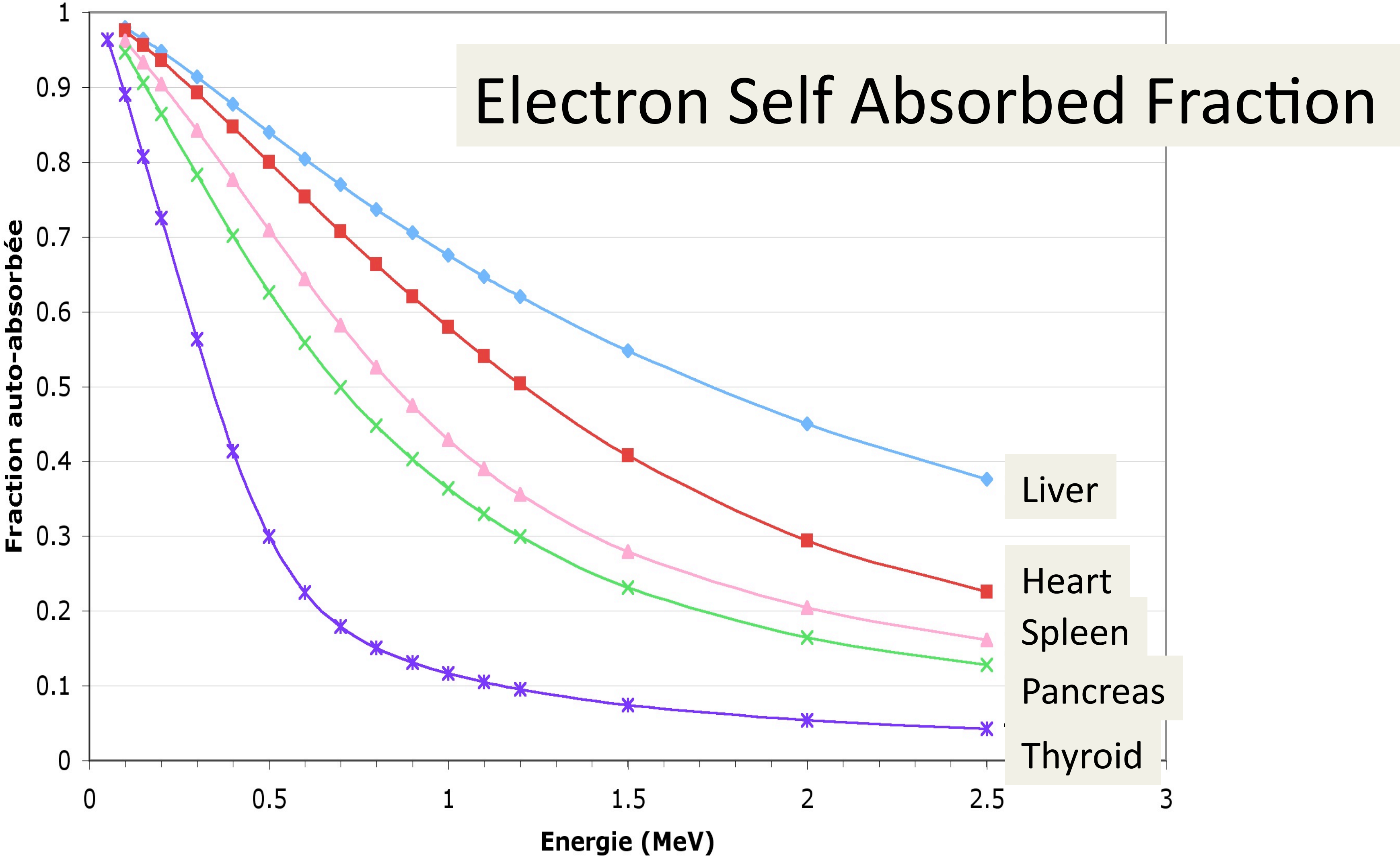


MCNP Input file

Organes cibles	Organes sources pour I-131										Facteurs S en Gy/(Bq.s)
	Vessie	Cerveau	Carcasse	Coeur	Reins	Foie	Poumons	Pancréas	Rate	Estomac	Os
Vessie	1,26E-10	4,42E-15	2,15E-13	1,58E-14	7,04E-14	3,92E-14	1,64E-14	4,58E-14	4,03E-14	3,75E-14	4,58E-14
Cerveau	4,57E-15	5,81E-11	1,03E-13	3,40E-14	8,01E-15	1,37E-14	3,08E-14	6,32E-13	8,58E-15	1,15E-14	6,32E-13
Carcasse	2,17E-13	1,02E-13	1,49E-12	1,45E-13	1,66E-13	1,27E-13	2,82E-13	3,36E-13	2,28E-13	1,28E-13	3,36E-13
Yeux	5,75E-15	3,45E-13	5,20E-13	2,15E-14	2,75E-15	1,13E-14	1,73E-14	1,18E-13	5,43E-15	5,60E-15	1,18E-13
Cœur	1,56E-14	3,40E-14	1,46E-13	1,05E-10	3,17E-14	2,60E-13	4,54E-12	1,19E-13	4,27E-14	7,13E-14	1,19E-13
Reins	6,97E-14	7,67E-15	1,65E-13	3,13E-14	4,76E-11	2,60E-13	3,98E-14	4,39E-14	4,28E-13	1,50E-13	4,39E-14
Foie	3,97E-14	1,35E-14	1,28E-13	2,65E-13	2,64E-13	1,21E-11	9,96E-13	1,21E-13	1,77E-13	7,02E-13	1,21E-13
Poumons	1,67E-14	3,16E-14	2,88E-13	4,57E-12	4,01E-14	1,01E-12	1,57E-10	1,60E-12	4,67E-14	8,27E-14	1,60E-12
Pancréas	5,67E-14	7,78E-15	2,65E-13	3,95E-14	2,90E-12	4,09E-13	4,35E-14	3,56E-14	4,48E-12	1,07E-12	3,56E-14
Rate	4,09E-14	8,71E-15	2,31E-13	4,15E-14	4,35E-13	1,76E-13	4,86E-14	6,24E-14	1,57E-10	2,02E-12	6,24E-14
Estomac	3,72E-14	1,10E-14	1,28E-13	7,16E-14	1,50E-13	7,01E-13	8,13E-14	5,04E-14	2,02E-12	1,04E-10	5,04E-14
Testicules	1,81E-13	3,18E-15	2,55E-13	8,29E-15	2,97E-14	1,73E-14	9,66E-15	5,18E-14	2,12E-14	1,94E-14	5,18E-14
Os	4,75E-14	6,05E-13	3,22E-13	1,18E-13	4,58E-14	1,18E-13	1,51E-12	9,89E-12	6,08E-14	5,17E-14	9,89E-12

S factor tables

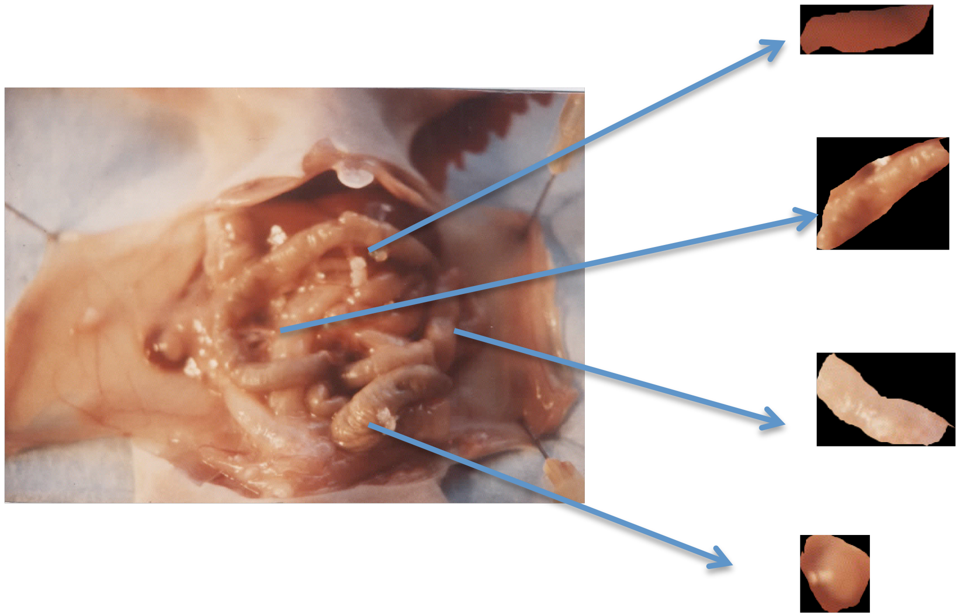
Calculation step



A Bitar et al. PMB 2007

Application to preclinical experiments

Gestin et al. J. Nucl. Med. 42; 146-, 2001

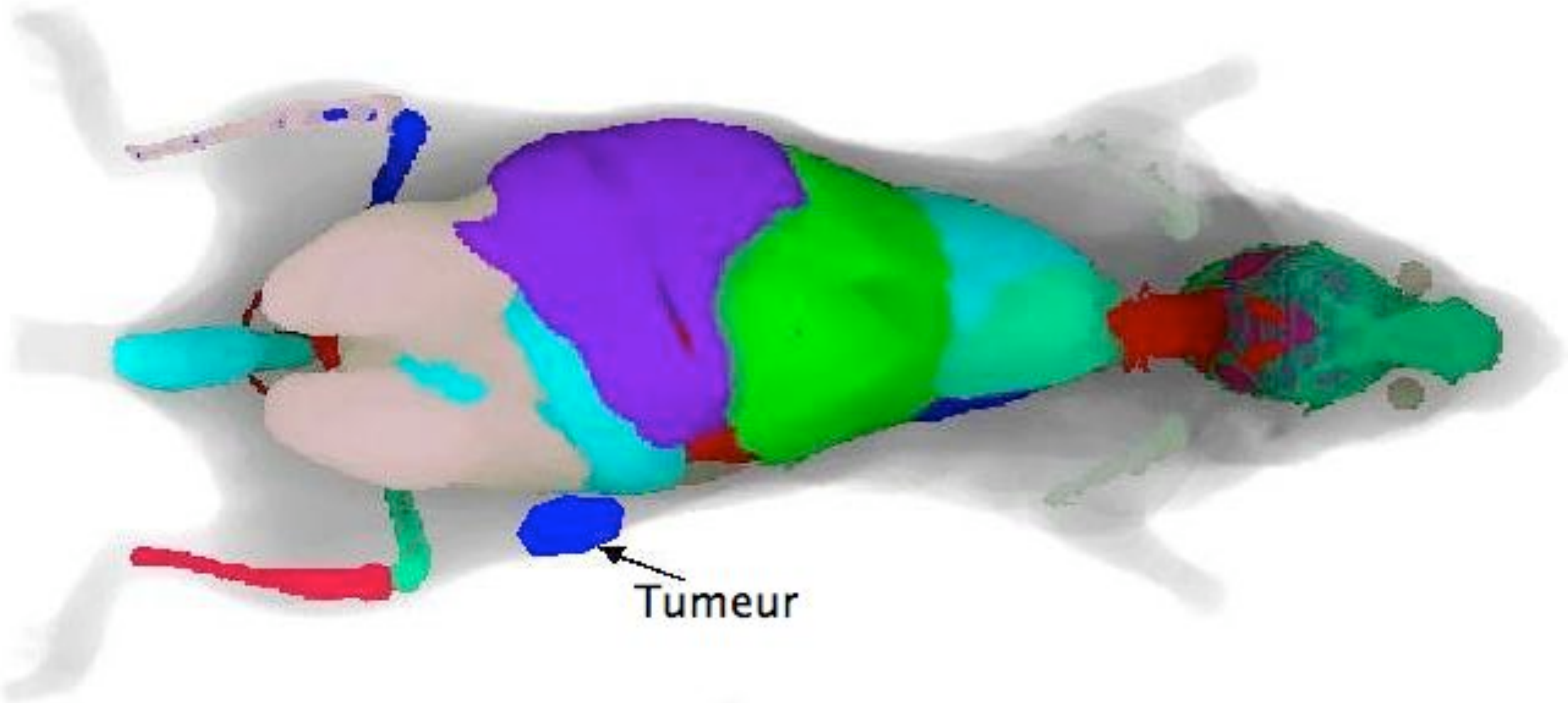


^{188}Re and ^{131}I:

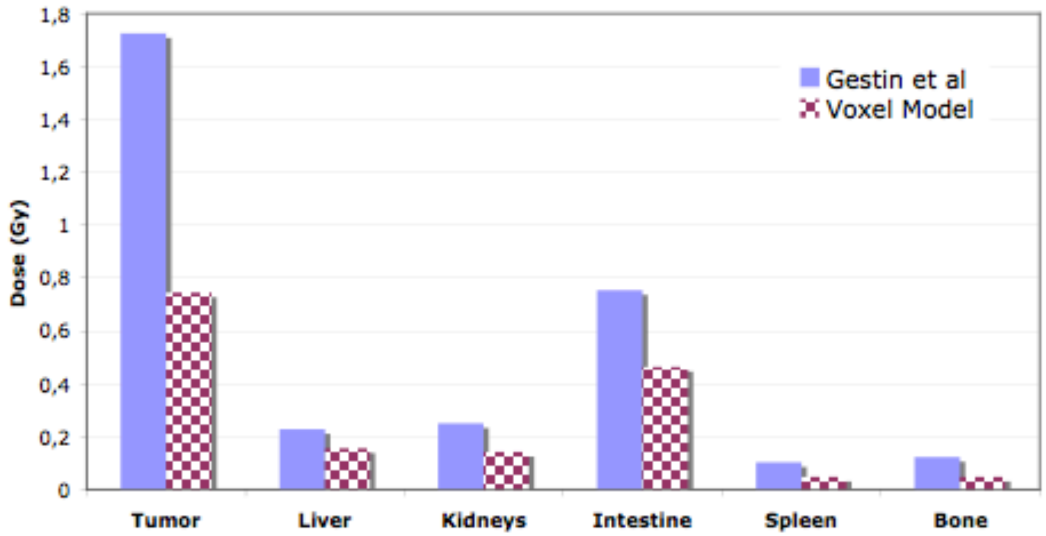
non-penetrating radiations

$$\overline{D}_{(h\leftarrow h)} = \frac{\tilde{A}_h \cdot \Delta}{m_h}$$

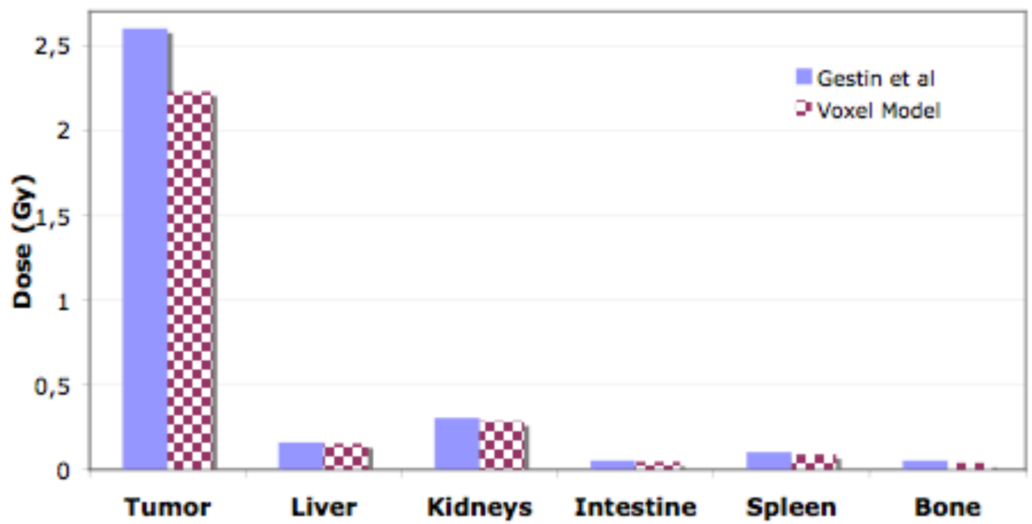
Adding a tumour



Results



^{188}Re



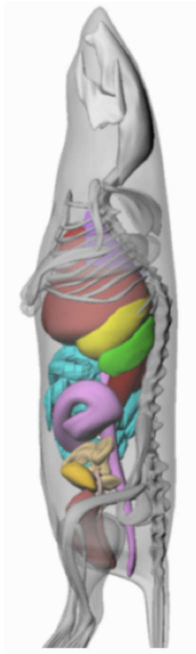
^{131}I

A Bitar et al. QJNM 2007

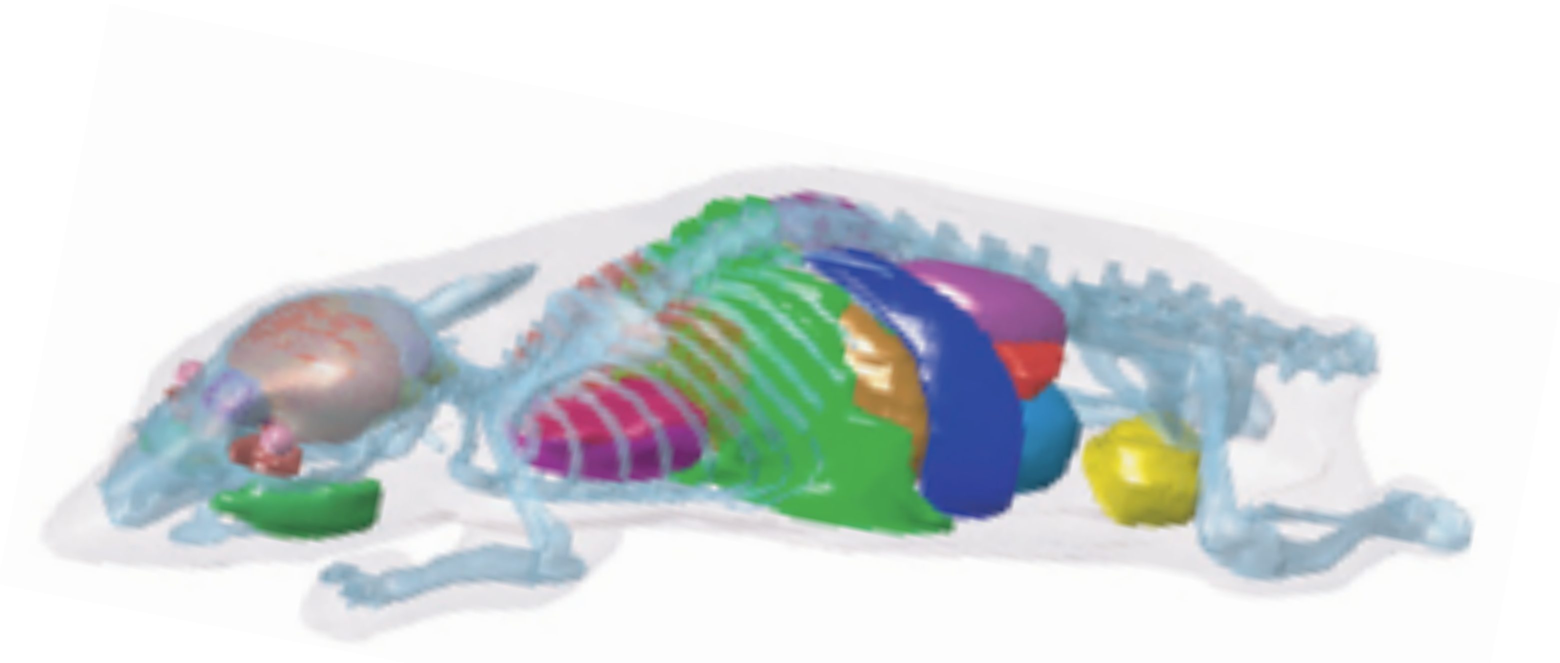
Question:

- Does that make a “dosimetric model” ?
  - NO: from a single mouse
  - YES It can be used for experiments…
- What are the differences between ≠ models?
  - Comparison of published voxel models
  - A Bitar -> S Boutaleb

Mouse models

	 Stabin 2006	 Larsson 2007	 Bitar 2007
Atlas	*Stabin et al 2006*	*Segars 2003*	*Bitar et al 2007*
Strain	*"Transgenic"*	*C57BL/6*	*Swiss Nude*
Mass	*27-g*	*33-g*	*30-g*

New model



http://neuroimage.usc.edu/Digimouse.html

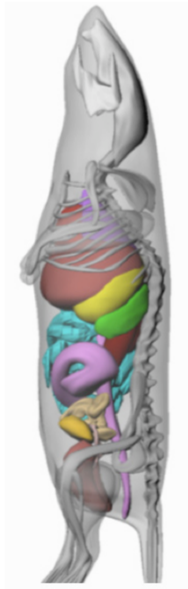
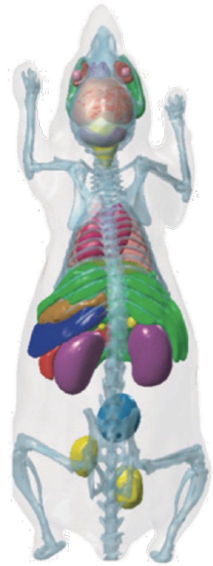
D.Dogdas et al 2007 Phys. Med. Biol
28g male nude mouse, 12 principal organs

+ MCNP -> MCNPX

Validation: MCNP vs. MCNPX

Organes cibles	Versions de MCNP	Organes sources *S en (Gy/Bq.s) pour ^{131}I*		
		Foie	Reins	Poumons
Foie	MCNP4c2	$1,60\ 10^{-11}$	$3,40\ 10^{-13}$	$1,56\ 10^{-12}$
	MCNPX	$1,60\ 10^{-11}$	$3,41\ 10^{-13}$	$1,53\ 10^{-12}$
	Difference %	-0,18	-0,07	1,77
Reins	MCNP4c2	$3,41\ 10^{-13}$	$7,48\ 10^{-11}$	$4,93\ 10^{-14}$
	MCNPX	$3,42\ 10^{-13}$	$7,51\ 10^{-11}$	$4,95\ 10^{-14}$
	Difference %	-0,34	-0,43	-0,50
Poumons	MCNP4c2	$1,58\ 10^{-12}$	$4,96\ 10^{-14}$	$1,58\ 10^{-10}$
	MCNPX	$1,55\ 10^{-12}$	$5,05\ 10^{-14}$	$1,59\ 10^{-10}$
	Difference %	1,73	-1,91	-0,93

Various dosimetric **voxel** models

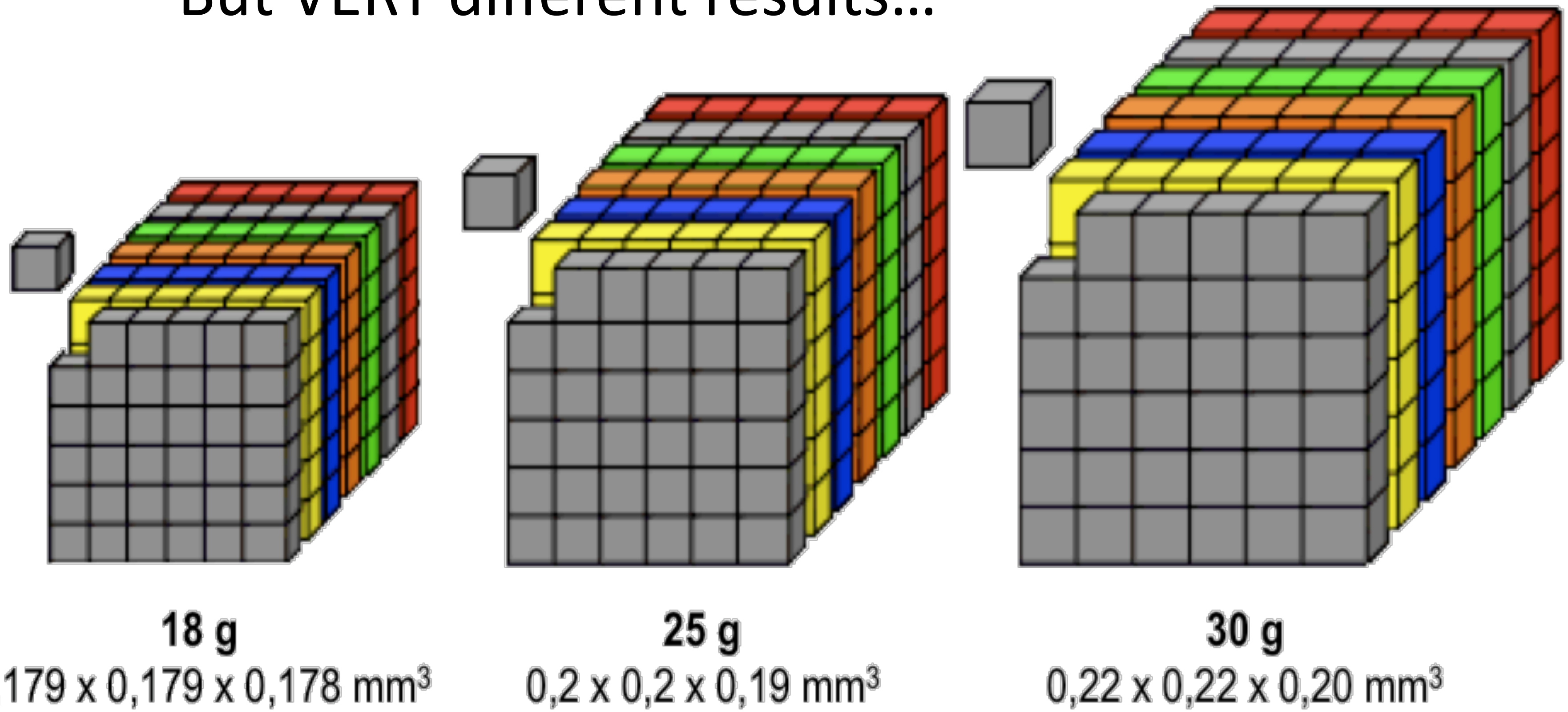
Dosimetric Models	 Stabin 2006	 Larsson 2007	 Bitar 2007	 Boutaleb 2009
Atlas	*Stabin et al 2006*	*Segars 2003*	*Bitar et al 2007*	*Dogdas et al 2007*
Souche	*"Transgenic"*	*C57BL/6*	*Swiss Nude*	*Swiss Nude*
Mass	*27-g*	*33-g*	*30-g*	*28-g*
Matrix	*256x256x256*	*128x432x128*	*220x450x111*	*190x496x104*
Voxel (mm)	*0.2x0.2x0.2*	*0.25x0.25x0.25*	*0.220x0.220x0.2*	*0.2x0.2x0.2*

Comparison of 2 models

Organes cibles	Modèles masse originale	Organes sources S en (Gy/Bq.s) pour ^{131}I		
		Foie	Reins	Poumons
Foie	Femelle 30 g	$1,60\ 10^{-11}$	$3,41\ 10^{-13}$	$1,53\ 10^{-12}$
	Mâle 28 g	$1,21\ 10^{-11}$	$2,64\ 10^{-13}$	$9,96\ 10^{-13}$
	Différence %	32,23	29,17	53,61
Reins	Femelle 30 g	$3,42\ 10^{-13}$	$7,51\ 10^{-11}$	$4,95\ 10^{-14}$
	Mâle 28 g	$2,60\ 10^{-13}$	$4,76\ 10^{-11}$	$3,98\ 10^{-14}$
	Différence %	31,54	57,77	24,37
Poumons	Femelle 30 g	$1,55\ 10^{-12}$	$5,05\ 10^{-14}$	$1,59\ 10^{-10}$
	Mâle 28 g	$1,01\ 10^{-12}$	$4,01\ 10^{-14}$	$1,57\ 10^{-10}$
	Différence %	53,47	25,94	1,27

Scaling problem?

- 2 Nude mice
- 28 vs. 30g
  - But VERY different results…



Adjusting for total mass

Masses des organes (*g*) pour les modèles à 27 g			
Organes	mâle adapté	Femelle adaptée	*Stabin et al.*
Foie	2,373	1,596	0,780
Estomac	0,264	0,382	0,298
Reins	0,586	0,338	0,334
Poumons	0,121	0,107	0,125
Coeur	0,264	0,246	0,143
Rate	0,164	0,189	0,022
Testicules	0,176	/	0,141

Table 3. Adaptation à 27g (équivalent *Stabin et al.*), des modèles mâle et femelle

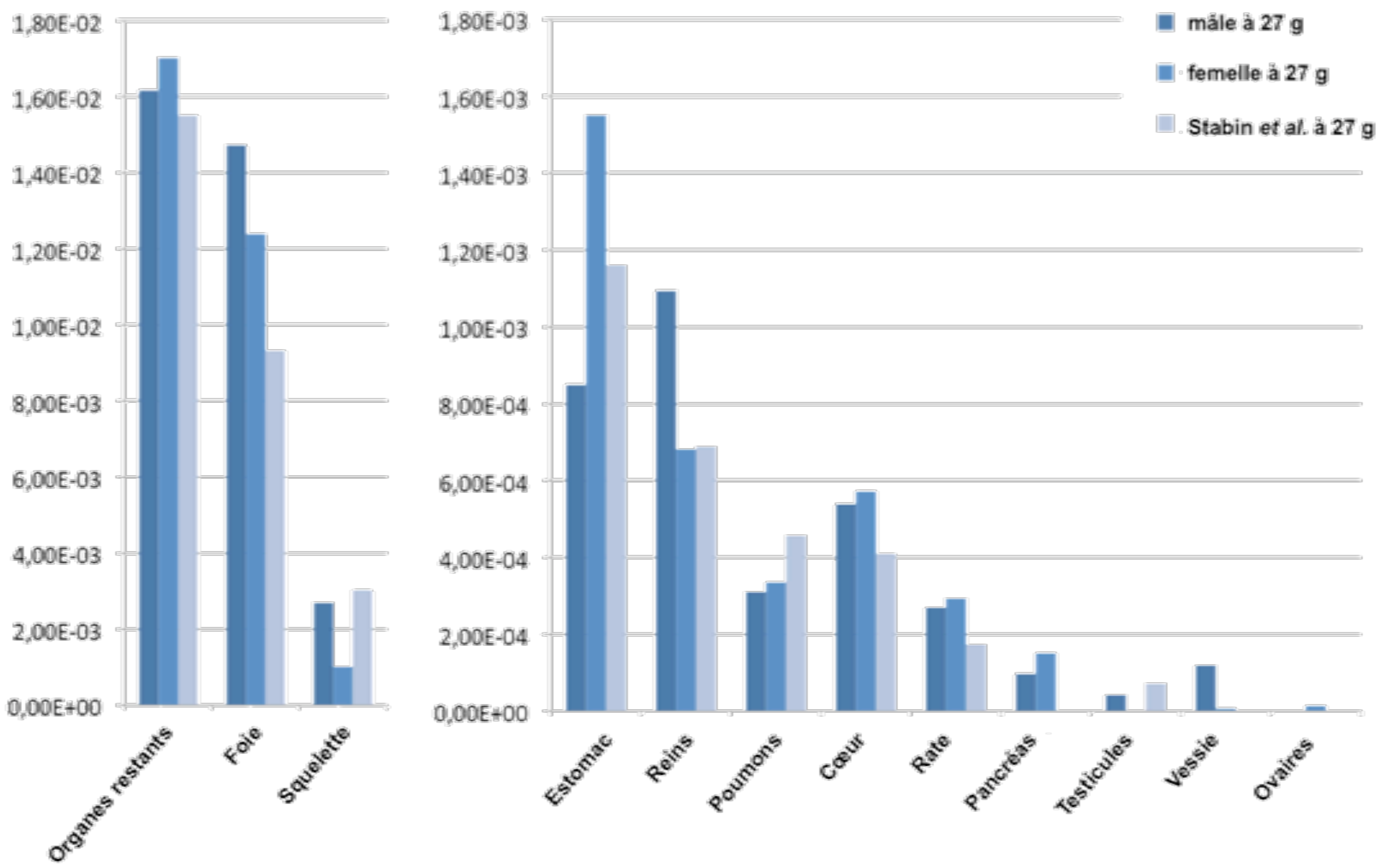
Adjusting for total mass

Masses des organes (*g*) pour les modèles à 33 g			
Organes	mâle adapté	Femelle adaptée	*Larsson et al.*
Foie	2,901	1,951	2,69
Estomac	0,323	0,466	/
Reins	0,717	0,413	0,415
Poumons	0,148	0,131	0,13
Coeur	0,323	0,300	0,12
Rate	0,201	0,231	0,13
Testicules	0,215	/	0,4

Table 4. Adaptation à 33g (équivalent *Larsson et al.*), des modèles mâle et femelle

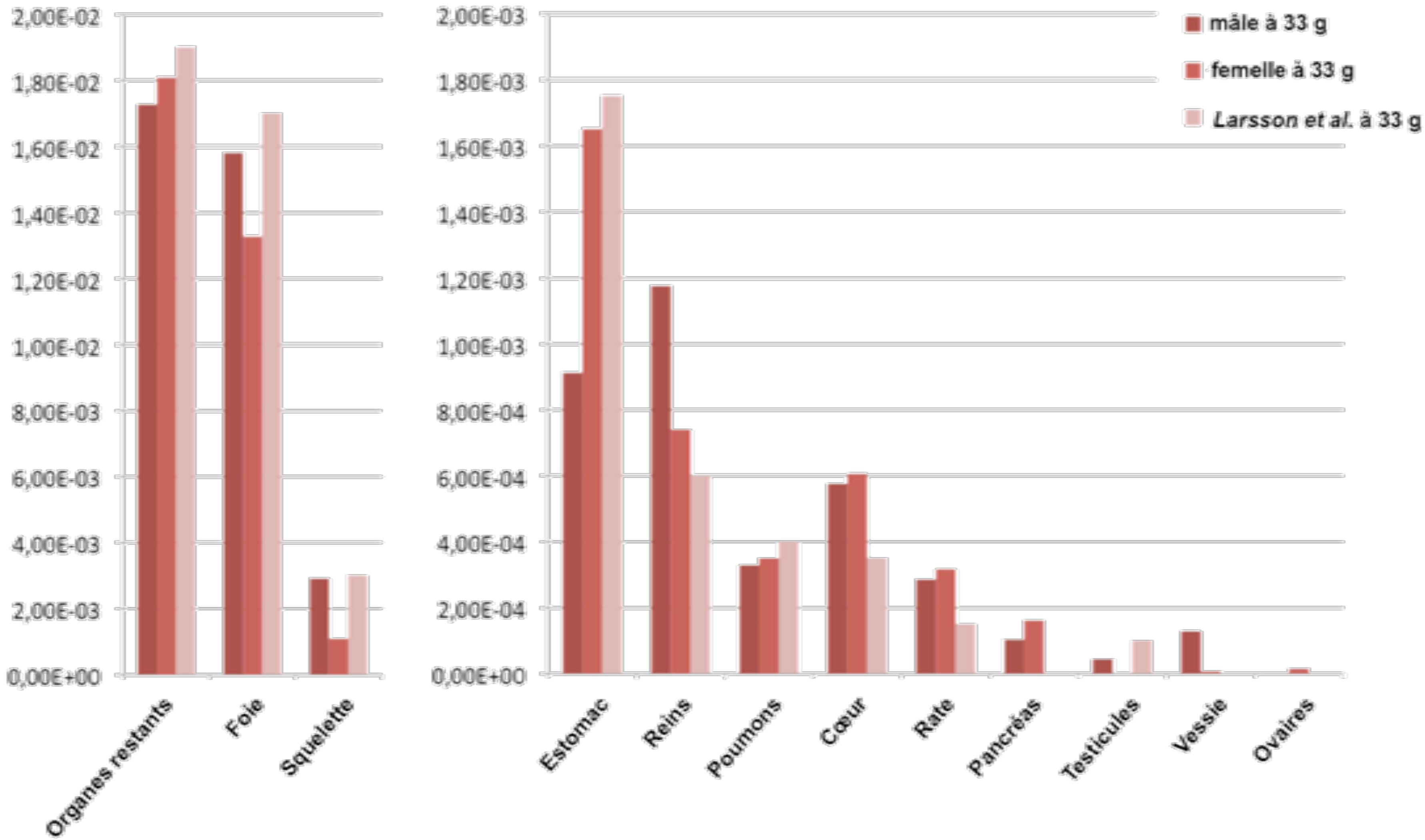
AFs for 100 keV photons emitted in liver

27g models



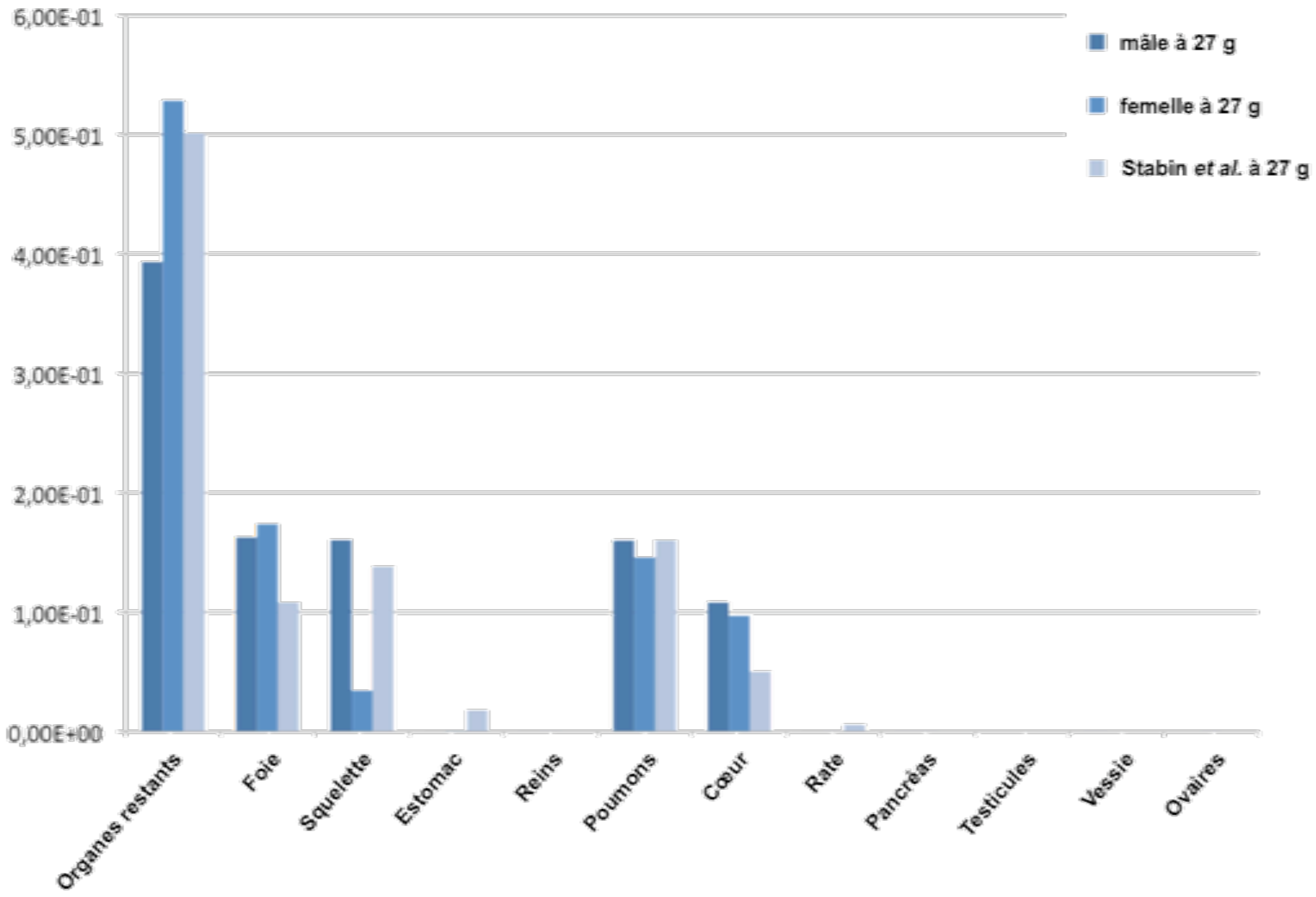
AFs for 100 keV photons emitted in liver

33g models



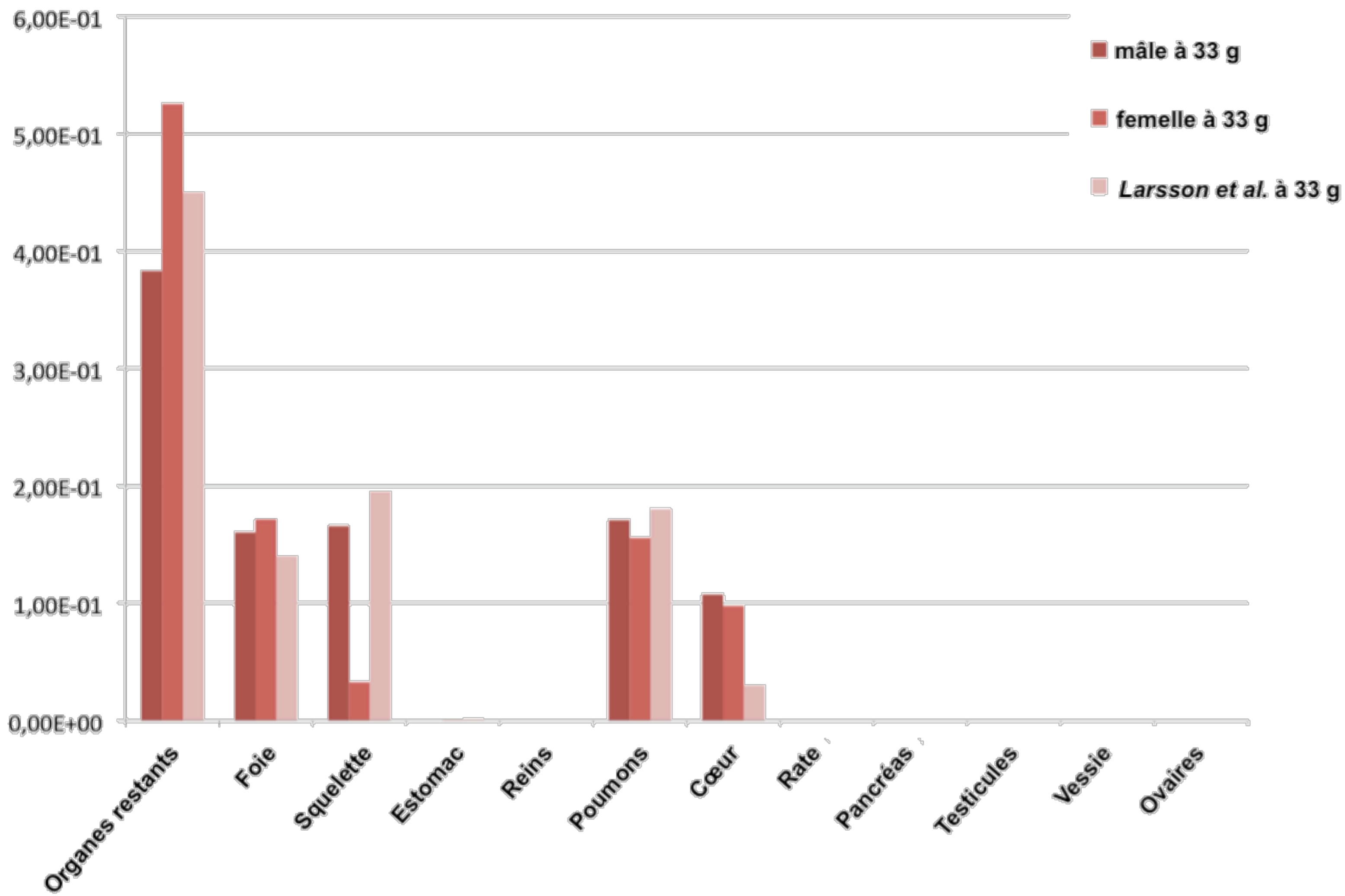
AFs for 1 MeV electrons emitted in lungs

27g models



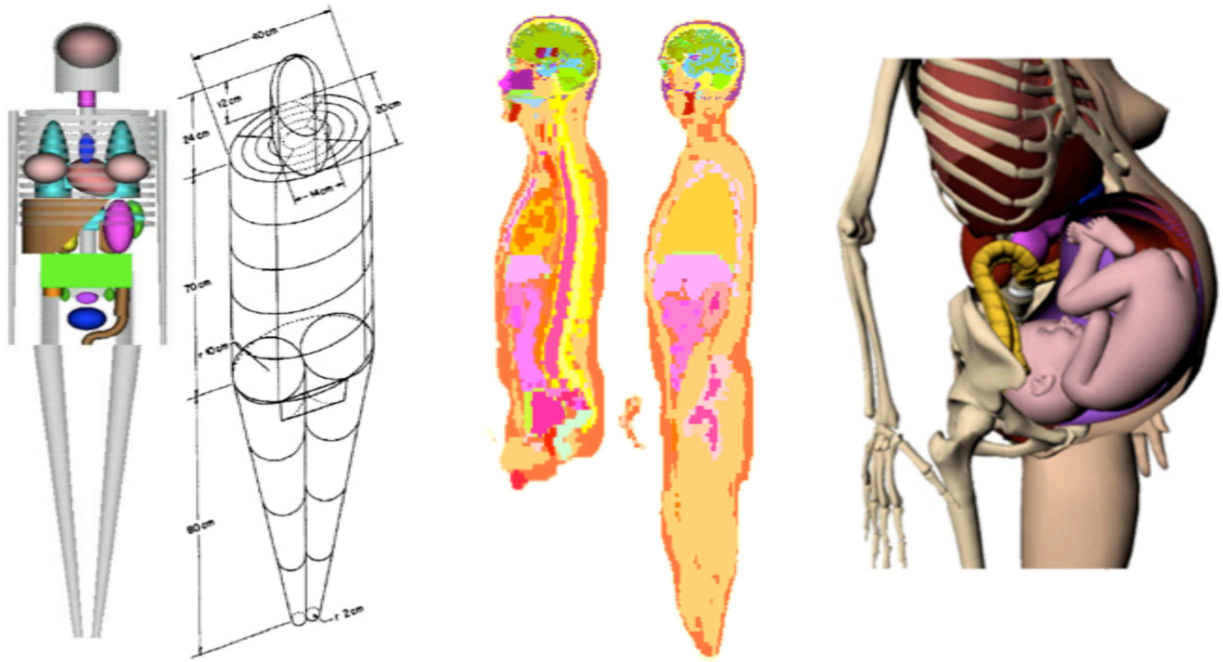
AFs for 1 MeV electrons emitted in lungs

33g models



Back to the concept of “model”

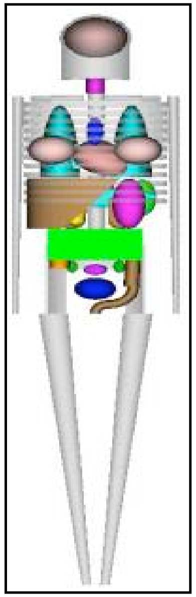
- The MIRD phantoms are far from realty
- They can be used as a reference
- They can be adjusted (mass ratio)
- There can be other models (voxel-based)



Mathématique Voxélisé Équations *NURBS*

Standard S values Vs. Specific S values for iodine 131

Adult Mathematical model
(ORNL/8381)

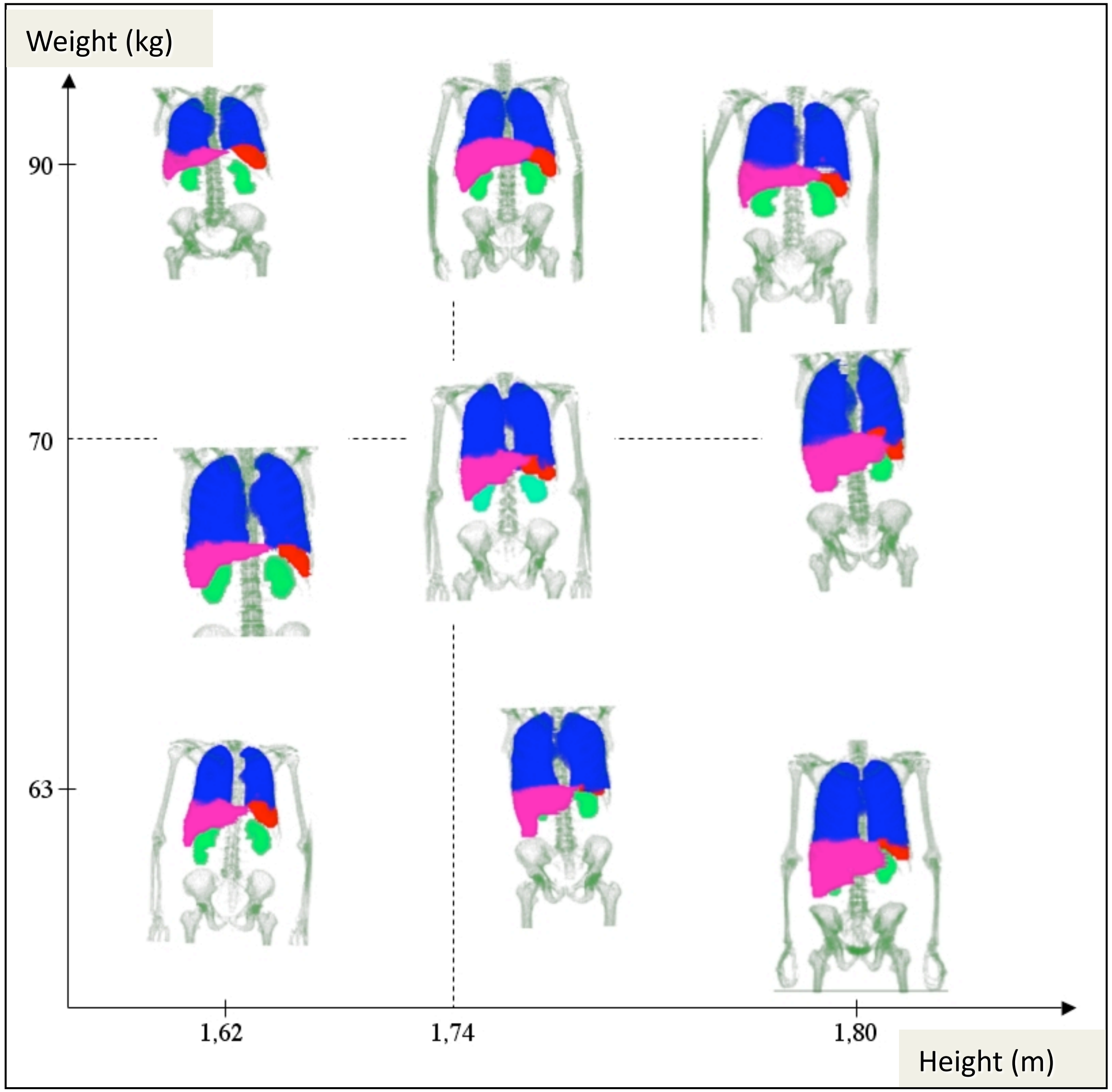


Height = 1,74 m

Weight = 70 kg

MIRDOSE3

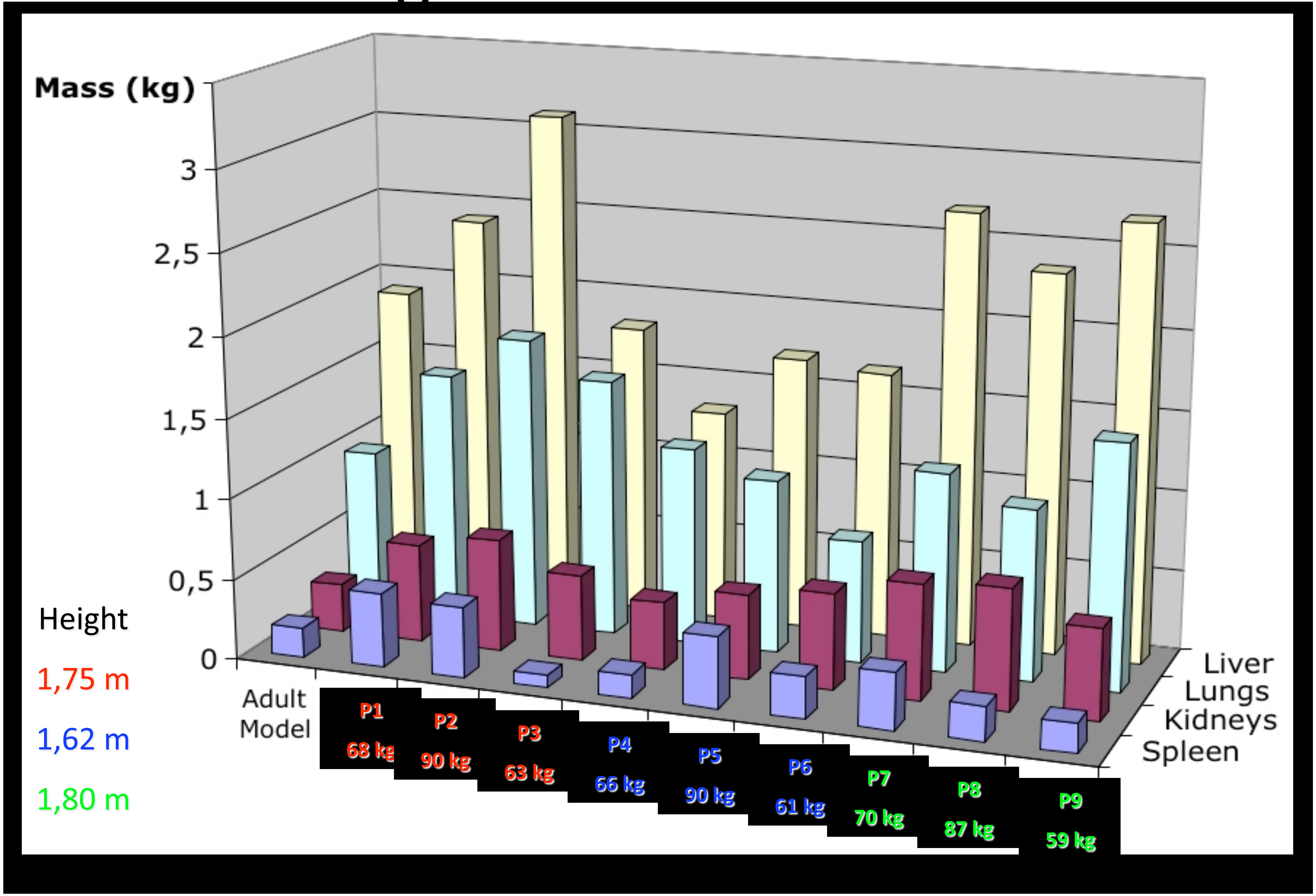
Vs.



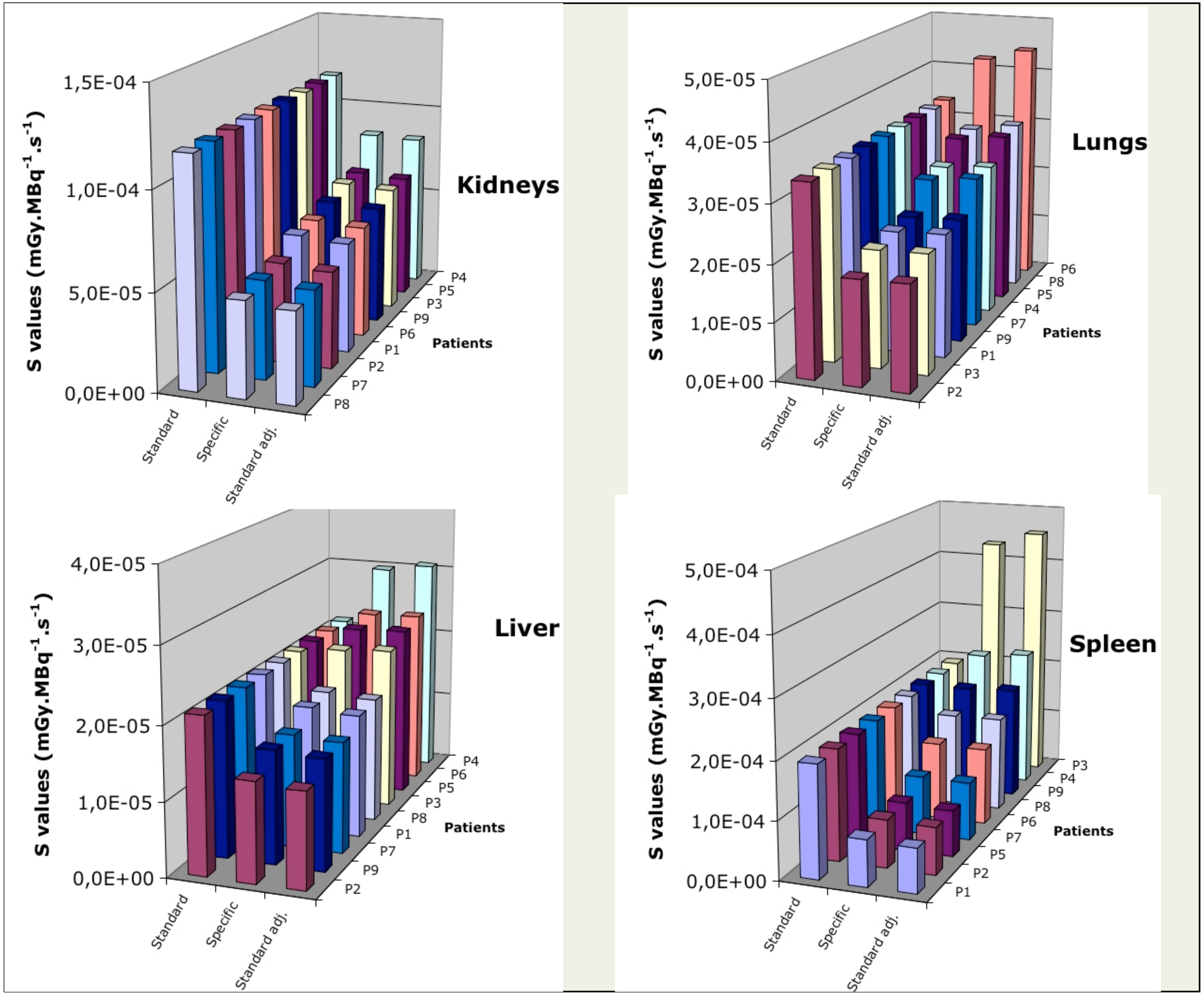
OEDIPE (MCNPX)

Chiavassa et al. EANM 2005; Divoli et al. J Nucl Med 2009; 50:316–323

Organ Mass Variation



Self-irradiation



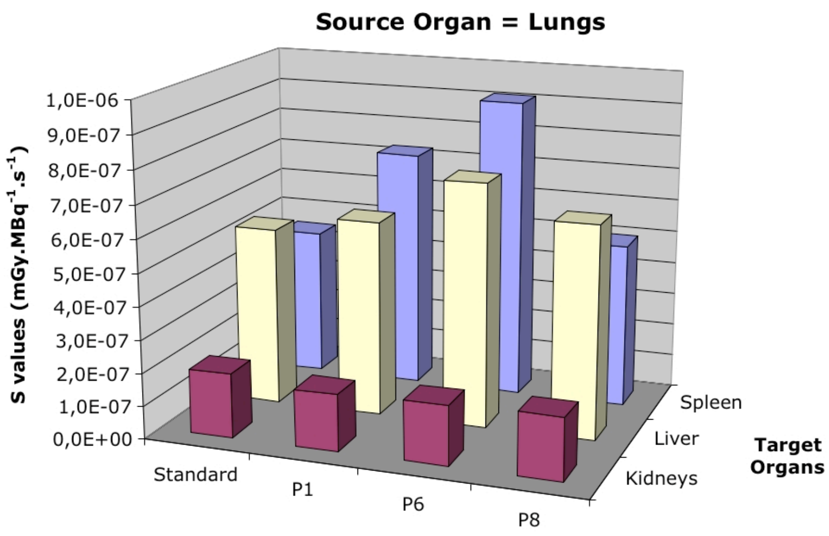
$S_{standard}$ / $S_{specific}$:

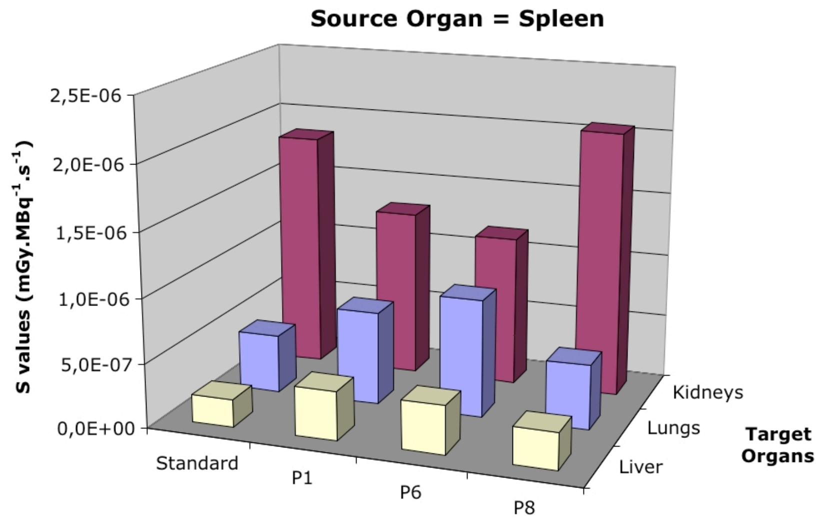
$0.45 \leq$ Ratio ≤ 2.43

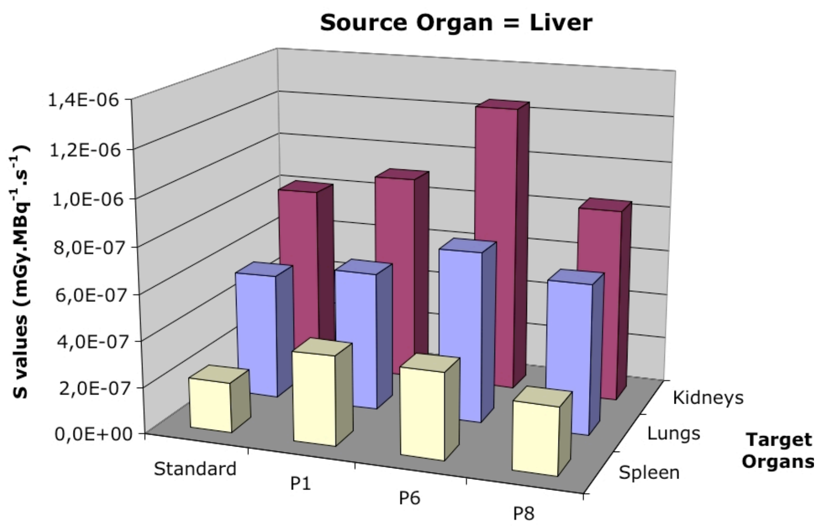
$S_{adjusted}$ / $S_{specific}$:

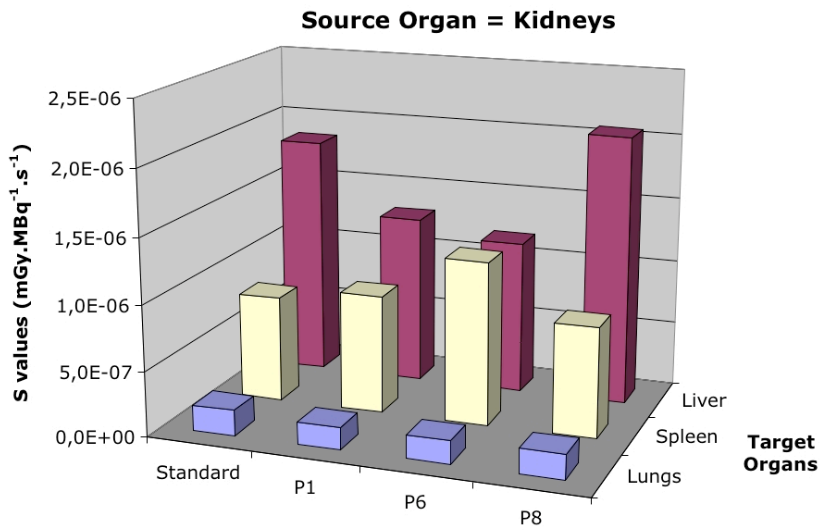
$0.96 \leq$ Ratio ≤ 1.06

Cross irradiation









Conclusion/human dosimetry

- Patients ≠ phantoms
- S factors are therefore ≠
- Self-irradiation S factors can be adjusted as long as THE MASS of the organ is known (CT)
- Cross irradiation usually is << self irradiation

- AS LONG AS MEAN DOSE IS OK, it should be possible to adjust S factors for clinical dosimetry

Back to mice…

$$S(r_S \leftarrow r_S)_{\exp} = S(r_S \leftarrow r_S)_{\text{mod}} \cdot \left(\frac{M_{\text{mod}}}{M_{\exp}}\right)$$

^{131}I

Organes cibles		Organes sources *S en (Gy/Bq.s) pour ^{131}I*		
		Foie	Reins	Poumons
Foie	28 g	1,21 10^{-11}	2,64 10^{-13}	9,96 10^{-13}
	Ref Bitar	1,15 10^{-11} *	3,41 10^{-13}	1,53 10^{-12}
	Difference %	4,91	-22,58	-34,90
Reins	28 g	2,60 10^{-13}	4,76 10^{-11}	3,98 10^{-14}
	Ref Bitar	3,42 10^{-13}	4,64 10^{-11} *	4,95 10^{-14}
	Difference %	-23,98	2,49	-19,60
Poumons	28 g	1,01 10^{-12}	4,01 10^{-14}	1,57 10^{-10}
	Ref Bitar	1,55 10^{-12}	5,05 10^{-14}	1,50 10^{-10} *
	Difference %	-34,84	-20,59	5,86

Table 5. Pondération par la masse des S pour ^{131}I

Back to mice...

$$S(r_S \leftarrow r_S)_{\exp} = S(r_S \leftarrow r_S)_{\mathrm{mod}} \cdot \left(\frac{M_{\mathrm{mod}}}{M_{\exp}} \right)$$

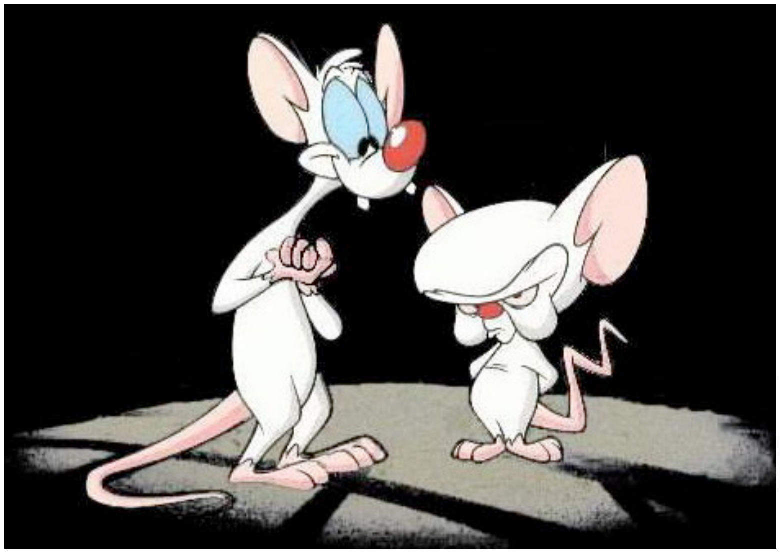
^{90}Y

Organes cibles		Organes sources S en (Gy/Bq.s) pour ^{90}Y		
		Foie	Reins	Poumons
Foie	28 g	4,11 10^{-11}	3,92 10^{-12}	9,64 10^{-12}
	Ref mâle	3,73 10^{-11} *	4,60 10^{-12}	1,36 10^{-11}
	Difference %	10,25	-14,94	-29,13
Reins	28 g	3,94 10^{-12}	1,36 10^{-10}	7,98 10^{-16}
	Ref mâle	4,62 10^{-12}	1,95 10^{-10} *	2,29 10^{-14}
	Difference %	-14,53	-30,35	-96,51
Poumons	28 g	9,82 10^{-12}	7,03 10^{-16}	2,00 10^{-10}
	Ref mâle	1,42 10^{-11}	4,96 10^{-14}	1,85 10^{-10} *
	Difference %	-30,84	-98,58	8,15

Table 6. Pondération par la masse des S pour ^{90}Y

Conclusion / mice dosimetry

- Different mice strain, age, sex, weight…
- Different S factors
- The mass adjustment does not work for high energy emitters such as ^{90}Y…



Back to ≠ possibilities / Mice

$\tilde{A}(r_S, T_D)$	$S(r_T \leftarrow r_S)$	$D(r_T, T_D)$
Group	model	model
~~Specific~~	~~Model ± adjusted~~	~~Model + realistic~~
Specific	Specific	Specific

Back to ≠ possibilities

$\tilde{A}(r_S, T_D)$	$S(r_T \leftarrow r_S)$	$D(r_T, T_D)$
Group	model	model
Specific	Model ± adjusted	Model + realistic
Specific	Specific	Specific

Current experiments

- Batches of mice of the same strain, age, sex
- Can one mouse from the batch serve as a reference?
  - Yes: OK
  - No: …
    - Mean $\tilde{A}\left(r_S, T_D\right)$
    - Use a model to get $S\left(r_T \leftarrow r_S\right)$
    - Problem for absorbed dose / effect relationship?
    - WHICH MODEL?

Back to ≠ possibilities

$\tilde{A}(r_S, T_D)$	$S(r_T \leftarrow r_S)$	$D(r_T, T_D)$
Group	model	model
Specific	Model ± adjusted	Model + realistic
Specific	Specific	Specific

Future experiments

- Full “mouse-specific” dosimetry?

NanoSPECT/CT; Bioscan

Inveon Module TEP; Siemens

"mouse-specific" dosimetry?

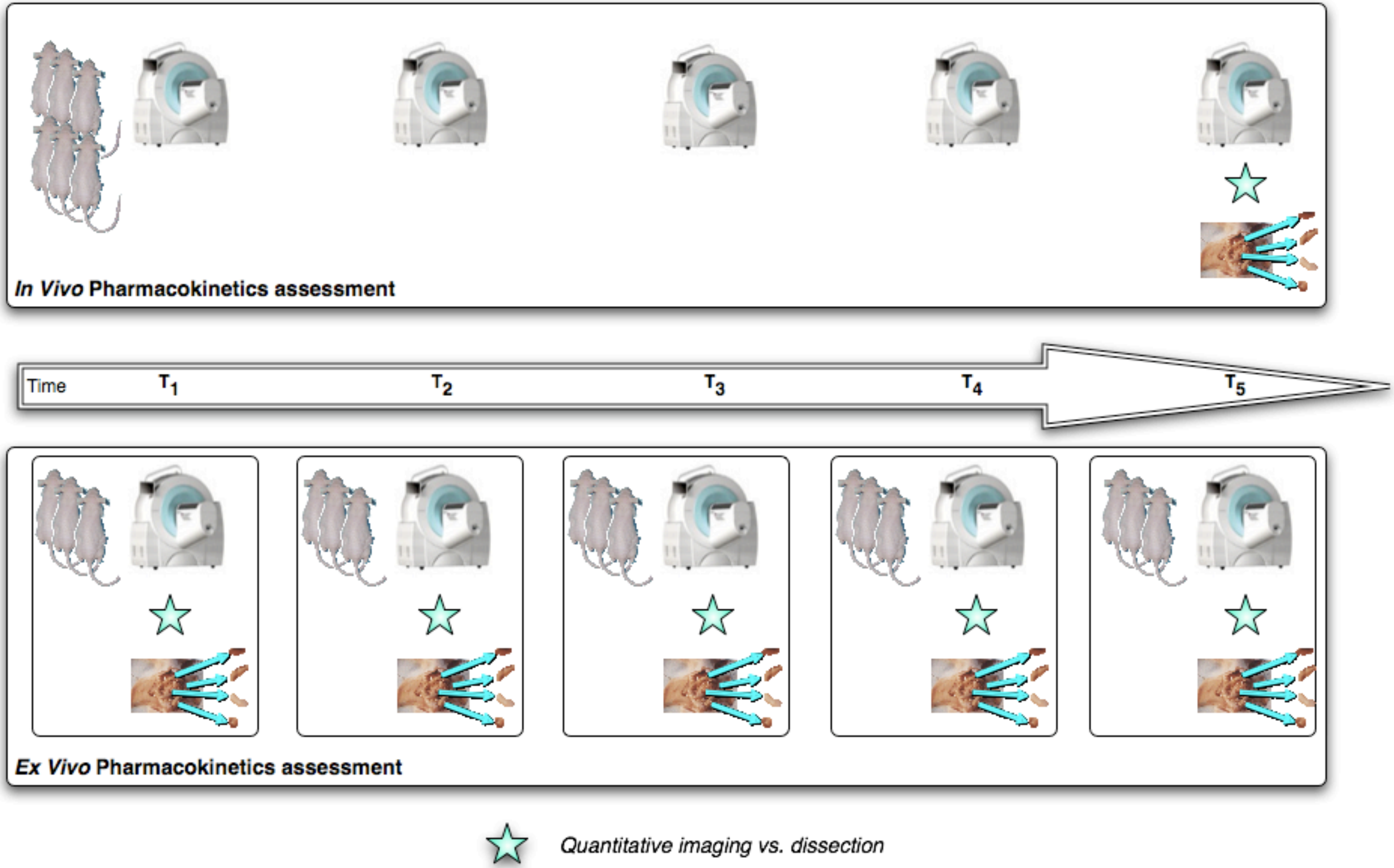
- Activity: now obtained from counting and averaging on several mice, at several time points
- Longitudinal studies:
  - One batch of mice is imaged several times to provide for "mouse-specific" $\tilde{A}\left(r_S, T_D\right)$
  - Calculation of specific $S\left(r_T \leftarrow r_S\right)$

» Mouse-specific $D\left(r_T, T_D\right)$

Problems to solve

- Anaesthesia -> OK
- Image fusion?
  - How to match images acquired at ≠ time-points
  - Use CT but CT-induced irradiation?
  - Scale (mm) ≠ from clinical imaging
- Time for mouse segmentation, S factor calculation, etc…
- Work in progress…

Work plan


In Vivo Pharmacokinetics assessment
Time
T1
T2
T3
T4
T5
Ex Vivo Pharmacokinetics assessment
Quantitative imaging vs. dissection

Thank you ☺