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RADIATION PROTECTION

ADDENDUM 4 TO ICRP PUBLICATION 53

Radiation Dose to Patients from Radiopharmaceuticals

A report of a Task Group of Committees 2 and 3 of the
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C
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Acetate

[1-^{11}C]Acetate

^{11}C

Biokinetic model

Acetate labelled with ^{11}C in the carboxyl position, [1-^{11}C]acetate, is used for dynamic PET studies of myocardial metabolism (Armbrecht *et al*., 1990; van den Hoff *et al*., 1996; Sun *et al*., 1997), and in renal (Schreeve *et al*., 1995), pancreatic (Shreve and Gross, 1997) and nasopharyngeal disease (Yeh *et al*., 1999).

In most tissues, after extraction from the blood, [1-^{11}C]acetate is activated to acetyl co-enzyme A (CoA) and enters the tricarboxylic acid (TCA) cycle. From the TCA cycle the label is lost mainly in the form of $^{11}CO_2$ (Armbrecht *et al*., 1990). In resting myocardium the behaviour of [1-^{11}C]acetate can be summarized as follows (Armbrecht *et al*., 1990):

- extraction of about two-thirds of the activity in a single capillary transit,
- a very rapid initial washout phase ($T_{½}$ < 5 sec),
- activation of [1-^{11}C]acetate to [1-^{11}C]acetyl-CoA within a few seconds,
- labelling of TCA cycle intermediates takes several minutes,
- onset of rapid $^{11}CO_2$ release after 2-3 min,
- $^{11}CO_2$ release is bi-exponential.

In all the tissues studied, the peak uptake appears to be reached within less than 3 minutes. After 3-5 min 50% of the tissue activity is present as $^{11}CO_2$; 24% as non-ionized species and 13% each as acetate and TCA-amino acid intermediates (Sun *et al*., 1997). The rate of metabolism of the radiopharmaceutical reflects the rate of oxidative metabolism in the tissue, and thus the oxygen supply.

Clinical studies indicate that in both myocardium and kidney parenchyma, the initial uptake is complete by 2.5-3.0 minutes post-injection and that between 3 and 30 min the ^{11}C is lost from the tissues with half-time of ~10 min. In normal pancreas the uptake is also complete in 3 min, and up to 30 min, at least, the activity is lost from the tissue with a half-time of 38 min. In the liver, uptake is again rapid, peaking at ~3 min, thereafter the loss ^{11}C from the tissue follows a tri-exponential clearance, with 35% being cleared with a half-time of 10 minutes and the remainder with half-times of 1 (30%) and 2 hours (35%) respectively.

Few data on the fractional deposition of [^{11}C]acetate in human tissues appear to be available in the literature. However, since there is a high extraction rate for [1-^{11}C]acetate in most tissues and its rate of metabolism reflects the tissue oxygen supply, the rate of blood flow, expressed as a fraction of the cardiac output, in the tissue might be used as an approximation of the tissue uptake of [1-^{11}C]acetate. Leggett and Williams (1995) have tabulated blood flow data for most human tissues, and these values have been used to construct the biokinetic model illustrated below. In this model, uptake in all tissues is assumed to be rapid with a half-time of 1 min.

References for [1-^{11}C]acetate

Armbrecht, J. J., Burton, D. B., Schelbert, H. R. (1990). Validation of [1-^{11}C]acetate as a tracer for non-invasive assessment of oxidative metabolism with positron emissin tomography in normal, ischemic, postischemic and hyperaemic canine myocardium. *Circulation* **81**, 1594-1605.

van den Hoff, J., Burchert, W., Wolpers, H. G., Meyer G. J., Hundeshagen, H. (1996). A kinetic model for cardiac PET with [1-^{11}C]acetate. *J. Nucl. Med*. **37**, 521-529.

Leggett, R. W., Williams, L. R. (1995). A proposed blood circulation model for reference man. *Health Phys*. **69**, 187-201.

Shreve, P., Chiao, P. C., Humes, H. D., Schwaiger, M., Gross, M. D. (1995) Carbon-11-acetate PET imaging in renal disease. *J. Nucl. Med*. **36**, 1595-1601.

Shreve, P. D. Gross, M. D. (1997). Imaging of the pancreas and related diseases with PET carbon-11-acetate. *J. Nucl. Med*. **38**, 1305-1310.

Sun, K. T., Chen, K., Huang, S-C., Buxton, D. B., Hansen, H. W., Kim, A. S., Siegel, S., Hoi, Y, Müller, P., Phelps, M. E., Schelbert, H. R. (1997). Compartment model for measuring myocardial oxygen consumption using [1-^{11}C]acetate. *J. Nucl. Med*. **38**, 459-466.

Yeh, S. H., Liu, R. S., Wu, L. C., Yen, S. H., Chang, C. W., Chen, K. Y. (1999). ^{11}C-acetate clearance in nasopharyngeal carcinoma. *Nucl. Med. Commun*, **20**, 131-134.

C
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Acetate

Biokinetic data

Organ (S)	F_s	$T_{½}$ (hours)	a	$\tilde{A}_s/A_0$ (hours)
Blood	1.0	0.017	1.0	0.023
Heart wall	0.045	–0.017	1.0	0.014
		0.17	0.50	
		8.0	0.50	
Kidneys	0.19	–0.017	1.0	0.059
		0.17	0.50	
		24	0.50	
Liver	0.25	–0.017	1.0	0.075
		0.17	0.35	
		1.0	0.30	
		2.0	0.35	
Pancreas	0.01	–0.017	1.0	0.0035
		0.67	0.50	
		2.0	0.50	
Other tissues	0.505	-0.017	1.0	0.15
		0.17	0.50	
		8.0	0.50	

This biokinetic model is not applicable for ^{14}C.

C
6
Acetate

Absorbed doses: [1-^{11}C]Acetate

^{11}C 20.38 min

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	3.5E-03	4.4E-03	6.8E-03	1.1E-02	1.8E-02
Bladder	1.2E-03	1.5E-03	2.4E-03	4.0E-03	7.2E-03
Bone surfaces	1.5E-03	2.0E-03	3.1E-03	4.9E-03	9.8E-03
Brain	1.0E-03	1.3E-03	2.1E-03	3.5E-03	6.7E-03
Breast	1.2E-03	1.5E-03	2.6E-03	4.1E-03	7.8E-03
Gall bladder	3.5E-03	4.0E-03	5.6E-03	9.0E-03	1.6E-02
GI tract					
Stomach	2.0E-03	2.4E-03	4.0E-03	6.1E-03	1.1E-02
SI	1.8E-03	2.2E-03	3.6E-03	5.8E-03	1.1E-02
Colon	1.6E-03	2.0E-03	3.3E-03	5.2E-03	9.6E-03
(ULI	1.9E-03	2.3E-03	3.8E-03	5.9E-03	1.1E-02)
(LLI	1.3E-03	1.6E-03	2.6E-03	4.2E-03	7.7E-03)
Heart	1.3E-02	1.7E-02	2.7E-02	4.2E-02	7.6E-02
Kidneys	5.3E-02	6.4E-02	9.1E-02	1.3E-01	2.4E-01
Liver	1.4E-02	1.8E-02	2.8E-02	4.1E-02	7.7E-02
Lungs	2.4E-03	3.1E-03	4.9E-03	7.7E-03	1.5E-02
Muscles	1.4E-03	1.7E-03	2.7E-03	4.3E-03	8.2E-03
Oesophagus	1.5E-03	1.9E-03	2.9E-03	4.5E-03	8.3E-03
Ovaries	1.4E-03	1.8E-03	2.9E-03	4.7E-03	8.9E-03
Pancreas	1.2E-02	1.6E-02	3.3E-02	4.3E-02	9.2E-02
Red marrow	1.8E-03	2.2E-03	3.4E-03	5.2E-03	9.4E-03
Skin	1.0E-03	1.3E-03	2.1E-03	3.3E-03	6.5E-03
Spleen	2.9E-03	3.7E-03	5.9E-03	9.1E-03	1.6E-02
Testes	1.0E-03	1.3E-03	2.1E-03	3.3E-03	6.6E-03
Thymus	1.5E-03	1.9E-03	2.9E-03	4.5E-03	8.3E-03
Thyroid	1.3E-03	1.6E-03	2.7E-03	4.5E-03	8.6E-03
Uterus	1.4E-03	1.8E-03	2.8E-03	4.6E-03	8.6E-03
Remaining organs	1.4E-03	1.8E-03	2.8E-03	4.5E-03	8.2E-03
Effective dose (mSv/MBq)	**3.5E-03**	**4.4E-03**	**6.7E-03**	**1.0E-02**	**1.9E-02**

C
6
Methionine

L -[Methyl-^{11}C]-methionine

^{11}C

Biokinetic model

The amino acid L-[Methyl-^{11}C]-methionine can be applied in tumour diagnosis and to the study of protein synthesis using positron emission tomography (PET). Deloar *et al.*, (1998) reported quantitative PET studies on the distribution of L-[Methyl-^{11}C]-methionine in five healthy, male volunteers, aged 22 to 40 years. The data suggested that about 90% of the activity was lost from all tissues during the first 90 minutes after injection; with biological half-times ranging from about 20 to 30 minutes. Thereafter the activity appeared to be lost more slowly, with a half-time that could be considered to be long in relation to the physical half-life of ^{11}C.

On the basis of the human data of Deloar *et al*., (1998) the biokinetic model presented below was developed. In the study of Deloar *et al.*, the uptake of L-[Methyl-^{11}C]-methionine into the brains of the 5 volunteers was estimated to be 2.8±0.7% of the injected activity, some 7 times higher than the value of 0.4% previously estimated by Comar *et al.*, (1976).

References for L -[Methyl-^{11}C]-methionine

Comar, D., Catron, J. C., Maziere, M., Marazanop, C. (1976). Labelling and metabolism of methionine-methyl-^{11}C. *Eur. J. Nucl. Med*. **1**, 11-14.

Deloar, H. M., Fujiwara, T., Nakamura, T., Itoh, M., Imai, D., Miyake, M. and Watanuki, S. (1998). Estimation of internal absorbed dose of L-[methyl-^{11}C]-methionine using whole body positron emission tomography. *Eur. J Nucl. Med*. **25**, 629-633.

C
6
Methionine

Biokinetic data

Organ (S)	F_s	$T_{½}$ (hours)	a	$\tilde{A}_S / A_O$ (hours)
Brain	0.030	0.4	0.90	0.0086
		12	0.10	
Kidneys	0.022	0.4	0.90	0.0063
		12	0.10	
Kidneys, excretion proc.				0.026
Liver	0.22	0.4	0.90	0.063
		12	0.10	
Lungs	0.05	0.4	0.90	0.014
		12	0.10	
Pancreas	0.016	0.4	0.90	0.0046
		12	0.10	
Spleen	0.010	0.4	0.90	0.0029
		12	0.10	
Gall bladder contents	0.077			0.0033
GI-tract				
Small intestine cont.	0.22			0.0055
ULI contents	0.22			0.00064
LLI contents	0.22			0.000024
Urinary bladder contents (all ages)	0.78			0.13
Other organs and tissues	0.652	0.4	0.90	0.19
		12	0.10	

This biokinetic model is not applicable for ^{14}C.

C
6
Methionine

Absorbed doses: L-[Methyl-^{11}C]-methionine

^{11}C 20.38 min

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	2.9E-03	3.6E-03	5.7E-03	8.9E-03	1.6E-02
Bladder	9.1E-02	1.2E-01	1.8E-01	2.7E-01	5.1E-01
Bone surfaces	1.7E-03	2.2E-03	3.4E-03	5.4E-03	1.1E-02
Brain	2.2E-03	2.2E-03	2.4E-03	2.8E-03	4.0E-03
Breast	1.3E-03	1.7E-03	2.7E-03	4.5E-03	8.8E-03
Gall bladder	1.1E-02	1.2E-02	1.6E-02	2.9E-02	9.6E-02
GI tract					
Stomach	2.1E-03	2.6E-03	4.3E-03	6.8E-03	1.3E-02
SI	3.3E-03	4.3E-03	7.1E-03	1.1E-02	2.1E-02
Colon	2.9E-03	3.7E-03	5.8E-03	9.0E-03	1.6E-02
(ULI	2.6E-03	3.3E-03	5.3E-03	8.4E-03	1.5E-02)
(LLI	3.4E-03	4.2E-03	6.5E-03	9.8E-03	1.7E-02)
Heart	1.9E-03	2.5E-03	4.0E-03	6.3E-03	1.2E-02
Kidneys	3.0E-02	3.6E-02	5.0E-02	7.4E-02	1.3E-01
Liver	1.1E-02	1.5E-02	2.3E-02	3.4E-02	6.4E-02
Lungs	4.5E-03	6.7E-03	9.5E-03	1.5E-02	2.9E-02
Muscles	1.9E-03	2.4E-03	3.8E-03	6.1E-03	1.2E-02
Oesophagus	1.5E-03	1.9E-03	3.0E-03	4.9E-03	9.5E-03
Ovaries	3.4E-03	4.3E-03	6.5E-03	1.0E-02	1.8E-02
Pancreas	1.3E-02	1.9E-02	3.9E-02	5.0E-02	1.1E-01
Red marrow	2.0E-03	2.5E-03	3.7E-03	5.5E-03	9.8E-03
Skin	1.3E-03	1.6E-03	2.6E-03	4.4E-03	8.6E-03
Spleen	5.7E-03	8.1E-03	1.2E-02	1.9E-02	3.6E-02
Testes	2.5E-03	3.4E-03	5.9E-03	9.3E-03	1.7E-02
Thymus	1.5E-03	1.9E-03	3.0E-03	4.9E-03	9.5E-03
Thyroid	1.3E-03	1.7E-03	2.8E-03	4.7E-03	9.3E-03
Uterus	5.7E-03	6.8E-03	1.1E-02	1.7E-02	2.9E-02
Remaining organs	2.3E-03	3.1E-03	4.9E-03	7.9E-03	1.3E-02
Effective dose (mSv/MBq)	**7.4E-03**	**9.7E-03**	**1.5E-02**	**2.2E-02**	**4.2E-02**

Bladder wall contributes to 61 % of the effective dose when the first voiding occurs after 3.5 hours.

Effective dose if bladder is emptied 1 or 0.5 hour after administration:

1 hour	6.3E-03	8.2E-03	1.3E-02	1.9E-02	3.7E-02
30 min	5.2E-03	6.8E-03	1.0E-02	1.6E-02	3.0E-02

F
9
F-DOPA

6-[^{18}F]-Fluoro-L-3,4,-dihydroxyphenylalanine (6-[^{18}F]Fluoro-L-dopa)

^{18}F

Biokinetic model

The amino acid analogue 6-fluoro-L-dopa (F-DOPA) is rapidly taken up into the human brain and transformed into the important catecholamine neurotransmitter dopamine (Luxen *et al.*, 1992, Pauwels *et al.*, 1994). After labelling with the positron-emitting radioisotope fluorine-18 the resulting ^{18}F-DOPA can be used for the scintigraphic investigation of normal and pathological dopamine metabolism in the human brain and in tumours (Luxen *et al.*, 1992, Meyer *et al.*, 1995, Heiss *et al.*,1996) and for the quantitative assessment of dopaminergic function in Parkinson's disease and other conditions.

Studies in normal human volunteers, and in dogs, after administration of ^{18}F-DOPA have shown that the activity is more or less uniformly distributed throughout the body tissues and is removed by a bi-exponential process with biological half- times of ~12 hours (67-94%) and 1.7 - 3.9 hours (6-33 %) (Harvey *et al.*, 1985, Boyes *et al.*, 1986). Both these half-times appear to be age-dependent (Harvey *et al.*, 1985). The ^{18}F is excreted through the kidneys, 50% with a half-time of 0.7 hours and 50% with a half-time of ~12 hours (Harvey *et al.*, 1985).

On the basis of the biokinetic data given by Harvey *et al*., (1985), and Dhawan *et al.*, (1996), the biokinetic model for ^{18}F-DOPA illustrated in the biokinetic data table was developed. This model assumes that, 100% of the ^{18}F is homogeneously distributed in the body and eliminated through the kidneys with biological half-times of 1 hour (50%) and 12 hours (50%). This model was, in spite of observations cited above, assumed to be independent of age.

Human studies have shown that the uptake of ^{18}F-DOPA in the striatum and cerebellum can be increased approximately two-fold by administration of the amino decarboxylase inhibitor carbidopa (Melega *et al.*, 1990, Hoffman *et al.*, 1992, Brown *et al.*, 1998).

References for 6-[^{18}F]-Fluoro-L-3,4,-dihydroxyphenylalanine (6-[^{18}F]Fluoro-L-dopa)

Boyes, R. E., Cumming, P., Martin, W. R. W., McGeer, E. G. (1986) Determination of plasma [^{18}F]-6-fluorodopa during positron emission tomography; elimination and metabolism in carbidopa treated subjects. *Life Sciences* **39**, 2243-2252.

Brown, W.D., Oakes, T.R., DeJesus, O.T., Taylor, M.D., Roberts, A.D. Nickles, R.J., Holden, J.E. (1998) Fluorine-18-fluoro-L-DOPA dosimetry with carbidopa pretreatment. *J. Nucl. Med.* **39**, 1884-1891.

Dhawan, V., Belakhlef, A., Robeson, W., Ishikawa, T., Margouleff, C., Takikawa, S., Chaly, T., Kazumata, K., Margouleff, D., Eidelberg, D. (1996) Bladder wall radiation dose in humans from fluorine-18-FDOPA. *J. Nucl Med.* **37**, 1850-1852.

Harvey, J., Firnau, G., Garnett, E. S. (1985) Estimation of the radiation dose in man due to 6-[^{18}F]Fluoro-L-Dopa. *J Nucl. Med.* **26**, 931-935.

Heiss, W.-D., Wienhard, K., Wagner, R, Lanfermann, H., Thiel, A., Herhoiz, K., Pietrak, U. (1996) F-DOPA as an amino acid tracer to detect brain tumors. *J Nucl. Med.* **37,** 1180-1182.

Hoffman, J. M., Melega, W. P., Hawk, T. C., Grafton, S. C., Luxen, A., Mahoney, D. K., Bardo, J. R., Huang, S.-C., Mazziotta, J. C., Phelps, M. E. (1992) The effects of carbidopa administration of 6-[^{18}F]fluoro-L-DOPA kinetics in positron emission tomography *J Nucl. Med*. **33,** 1472-1477.

Lu, E., Meyer, E., Kuwabara, H., Ma, Y., Shiraishi, M., Evans, A. C. (1995) Reduction of radiation absorbed dose in F-18-DOPA PET studies by hydration-induced voiding. *J. Nucl. Med.* **36** (Suppl.) 98P (Abstract).

Luxen, A, Guillaume, M., Melega, W. P., Pike, V. W., Solin, O., Wagner, R. (1992) Production of 6-[^{18}F]fluoro-L-DOPA and its metabolism in vivo - A critical review. *Nucl. Med. Biol.* **19,** 149-158.

Melega, W. P., Hoffman, J. M., Luxen, A., Nissenson, C. H. K., Phelps, M. E., Barrio, J. P. (1990) The effects of carbidopa on the metabolism of 6-[^{18}F]fluoro-L-dopa in rats, monkeys and humans. *Life Sciences* **47**, 149-157.

Meyer, G.-J., Waters, S. L., Coenen, H. H., Luxen, A., Maziere, B, Långström, B. (1995) PET radiopharmaceuticals in Europe: current use and data relevant for the formulation of summaries of product characteristics (SPCs). *Eur. J Nucl. Med.* **22,** 1420-1432.

Pauwels, T., Dethy, S., Goldman, S., Monclus, M., Luxen, A. (1994) Effect of catechol-O-methyl transferase inhibition on peripheral and central metabolism of 6- [^{18}F]Fluoro-L-DOPA. *Eur. J Pharmacol*. **257,** 53-58.

F
9
F-DOPA

Biokinetic data

Organ (S)	F_S	$T_{½}$(hours)	a	$\tilde{A}_S/A_O$(hours)
Total body	1.00	1	0.50	1.61
		12	0.50	
Kidneys	1.00			0.032
Urinary bladder	1.00			
Adults and 15 years				0.60
10 years				0.53
5 years and 1 year				0.37

F
9

F-DOPA

Absorbed doses: ^{18}F-DOPA

^{18}F 1.83 hours

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	9.6E-03	1.2E-02	1.9E-02	3.0E-02	5.5E-02
Bladder	3.0E-01	3.8E-01	5.1E-01	5.6E-01	1.0E+00
Bone surfaces	9.4E-03	1.2E-02	1.8E-02	2.7E-02	5.1E-02
Brain	7.0E-03	8.7E-03	1.4E-02	2.4E-02	4.4E-02
Breast	6.6E-03	8.4E-03	1.3E-02	2.0E-02	4.0E-02
Gall bladder	1.0E-02	1.2E-02	1.9E-02	2.8E-02	5.0E-02
GI tract					
Stomach	9.3E-03	1.1E-02	1.7E-02	2.7E-02	5.0E-02
SI	1.3E-02	1.6E-02	2.5E-02	3.5E-02	6.5E-02
Colon	1.5E-02	1.8E-02	2.6E-02	3.6E-02	6.3E-02
(ULI	1.2E-02	1.5E-02	2.2E-02	3.3E-02	5.9E-02)
(LLI	1.8E-02	2.1E-02	3.1E-02	4.1E-02	6.9E-02)
Heart	8.8E-03	1.1E-02	1.8E-02	2.7E-02	5.0E-02
Kidneys	2.5E-02	3.0E-02	4.2E-02	6.3E-02	1.1E-01
Liver	8.9E-03	1.1E-02	1.7E-02	2.8E-02	5.2E-02
Lungs	7.8E-03	1.0E-02	1.6E-02	2.4E-02	4.6E-02
Muscles	9.8E-03	1.2E-02	1.9E-02	2.8E-02	5.2E-02
Oesophagus	8.0E-03	1.0E-02	1.6E-02	2.5E-02	4.8E-02
Ovaries	1.7E-02	2.2E-02	3.1E-02	4.2E-02	7.4E-02
Pancreas	1.0E-02	1.2E-02	2.0E-02	3.0E-02	5.6E-02
Red marrow	9.7E-03	1.2E-02	1.8E-02	2.6E-02	4.7E-02
Skin	6.9E-03	8.4E-03	1.3E-02	2.1E-02	4.1E-02
Spleen	9.2E-03	1.2E-02	1.8E-02	2.8E-02	5.2E-02
Testes	1.3E-02	1.8E-02	2.8E-02	3.8E-02	7.1E-02
Thymus	8.0E-03	1.0E-02	1.6E-02	2.5E-02	4.8E-02
Thyroid	8.0E-03	1.0E-02	1.6E-02	2.7E-02	5.0E-02
Uterus	2.8E-02	3.3E-02	4.9E-02	6.1E-02	1.1E-01
Remaining organs	9.9E-03	1.2E-02	1.9E-02	2.8E-02	5.1E-02
Effective dose (mSv/MBq)	**2.5E-02**	**3.2E-02**	**4.5E-02**	**5.6E-02**	**1.0E-01**

Bladder wall contributes to 60 % of the effective dose when the first voiding occurs after 3.5 hours.

Effective dose if bladder is emptied 1 or 0.5 hour after administration:

1 hour	1.8E-02	2.3E-02	3.4E-02	4.7E-02	8.7E-02
30 min	2.0E-02	2.5E-02	3.6E-02	4.7E-02	8.8E-02