INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER
[^{18}F]FLUORMETHYLCHOLINE, DOCUMENTNUMBER 3007.1
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1. INTRODUCTION

The subject of this IMPD is the radiolabelled compound [^{18}F]fluoromethyl-dimethyl-2-hydroxyethylammonium also known as [^{18}F]fluoromethylcholine, [^{18}F]FMcholine and FCH.

Choline is an important component in the buildup of phospholipid cell membranes, hence fast proliferating cells may express high choline uptake. This property has been utilized in several positron emission tomography (PET) studies both with [*N-methyl*-^{11}C]choline and [^{18}F]fluoromethylcholine for the the detection and differential diagnosis of prostate cancer, breast carcinoma and brain tumors.

[^{18}F]Fluoromethylcholine is synthesized at the department of Nuclear Medicine and PET Research of the VUmc, Amsterdam. This lab has a government license for the manufacture of radiopharmaceuticals according to the EU directive on radiopharmaceuticals, EudraLex - Volume 4: Good manufacturing practice (GMP) Guidelines.

2.1 CHEMICAL PHARMACEUTICAL DATA

2.1.S DRUG SUBSTANCE

2.1.S.1 General Information

2.1.S.1.1 Nomenclature

[^{18}F]Fluoromethyl-dimethyl-2-hydroxyethylammonium; ([^{18}F]Fluoromethylcholine).

2.1.S.1.2 Structure

$C_5H_{13}ClFNO$, Mw = 157.61 g/mol

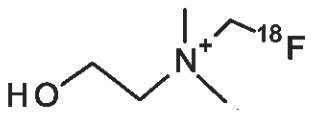

Figure 1: Chemical structure of [^{18}F]fluoromethylcholine

2.1.S.1.3 General Properties

[^{18}F]Fluoromethylcholine is obtained on a 'on column reaction' on a solid phase extraction column. The labelled compound is kept as 'solid' on the solid phase extraction column

2.1.S.2 Manufacture

2.1.S.2.1 Manufacturer(s)

^{18}F (as $^{18}F^-$)
Cyclotron BV
De Boelelaan 1083
1081 HV Amsterdam

^{18}F-Fluormethylcholine:
VU University Medical Centre
Dept of Nuclear Medicine & PET Research
De Boelelaan 1107
1081 HV Amsterdam
The Netherlands

Precursor: Dimethylaminoethanol:
Sigma-Aldrich Chemie B.V.
Postbus 27
3330 AA Zwijndrecht
The Netherlands

2.1.S.2.2 Description of Manufacturing Process and Process Controls

Cyclotron produced ^{18}F is extracted from the irradiated enriched water and worked up for a nucleophilic reaction with dibromomethane. After the fluorination reaction the product, fluorobromethane, is separated from the dibromomethane by distillation over silica cartridge columns. Subsequently the product, reacts on column with 2-(dimethylamino)-ethanol (DMAE), to [^{18}F]Fluormethylcholine, after which the product is ready for formulation.

Starting materials:

Precursor:

The precursor which is used for the production of [18F]Fluormethylcholine is 2-(dimethylamino)-ethanol (DMAE). Purity grade of this is "purified by redistillation, ≥99.5%". Certificate of analysis is given in appendix b.

18F:

This positron emitter with the half life of 109.8 minutes is produced by Cyclotron BV. and obtained as fluoride.

The labelling procedure is performed in a closed isolator class A with radiation protection for the employees in a class C background. To monitor the air-quality in the isolator, a settle plate is exposed during production process.

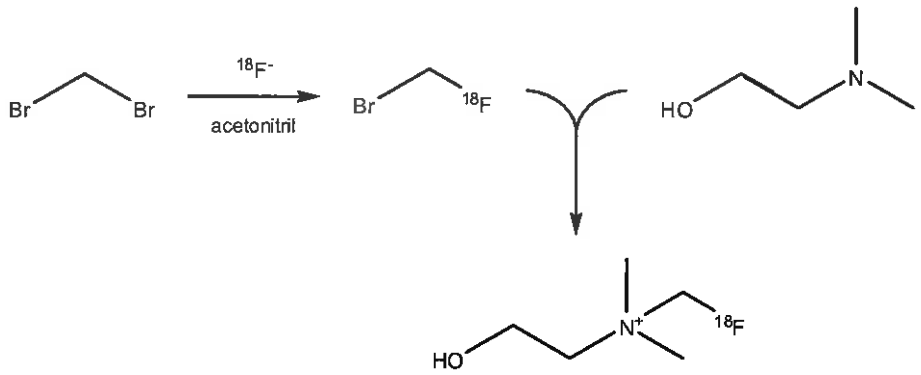

Figure 2: Reaction-scheme of [18F]fluoromethylcholine

2.1.S.2.3 Control of Materials

Table 1: Reagents, solvents and other materials

Material	Grade	
Dry acetonitril	≥ 99.9 %, max 10 ppm water	Merck
Kryptofix/Potassiumcarbonate solution in water for injection	Kryptofix: for synthesis ≥ 99.0 % Potassiumcarbonate: 99,995 % Water for injection: Ph Eur.	Merck Aldrich Hospital Pharmacy VUmc
50 % dibromomethane in acetonitril	≥ 99.0 %	Aldrich
Precursor 2-(dimethylamino)-ethanol (DMAE)	purified by redistillation, ≥99.5%, purity given in appendix b	Aldrich

Entrance control of reagents, solvents is performed according to SOP W8R-0011 and archived together with certificates of analysis of suppliers.

2.1.S.2.4 Controls of Critical Steps and Intermediates

Not applicable

2.1.S.2.5 Process Validation and/or Evaluation

Validation of manufacturing process

Before the product was applied to human at VU University Medical Centre, Amsterdam, three consecutive batches of [18F]Fluoromethylcholine were produced and tested according to all quality specifications. All the reports and descriptions are to be validated by the head of the production, and the head of quality assurance who are responsible for the production of the

radiopharmaceuticals. The most recent report concerning validation of the process is given in appendix c.

2.1.S.2.6 Manufacturing Process Development

The manufacturing processes for clinical supply will be done according to EU GMP guidelines in a dedicated certified, government licensed laboratory.

2.1.S.3 Characterization

2.1.S.3.1 Elucidation of Structure and Other Characteristics

Due to the radioactive nature of the drug substance, identification was made by analytical radio/refractometer-HPLC where the chromatographic retention time of the drug substance was compared with the non-radioactive authentic reference compound Fluoromethylcholine. Information concerning the quality and origin of the non-radioactive reference compound FMCholine is provided in section 2.1.S.5.

2.1.S.3.2 Impurities

Due to the radioactive nature, control impurities of the API is done as part of control of the drug product as described in section 2.1.P.5.

2.1.S.4 Control of Drug Substance

2.1.S.4.1 Specification

See section 2.1.P.5.1

2.1.S.4.2 Analytical Procedures

See section 2.1.P.5.2

2.1.S.4.3 Validation of Analytical Procedures.

See section 2.1.P.5.3

2.1.S.4.4 Batch Analyses

See section 2.1.P.5.4

2.1.S.4.5 Justification of specification

See section 2.1.P.5.6

2.1.S.5 Reference Standards or Materials

Reference compound FMCholine was provided by ABX, Germany.

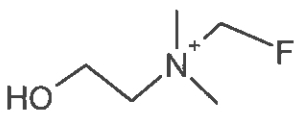

Figure 3: Chemical structure of FMCholine

2.1.S.6 Container Closure System

See section 2.1.P.7

2.1.S.7 Stability

See section 2.1.P.8

2.1.P DRUG PRODUCT

2.1.P.1 Description and Composition of the DRUG Product

The medicinal product is a clear, particle-free i.v. solution. 1 dose contains about 300-10000 MBq of [^{18}F]Fluoromethylcholine.

Table 2: Composition of a Batch of Drug Product [^{18}F]fluoromethylcholine
Each batch (15 ml) is composed as follows:

Name of ingredient	Concentration	Function	Reference to standard
Active ingredients [^{18}F]Fluoromethylcholine	20 – 666 MBq/ml	Active ingredient	In house
Other ingredients Sterile buffer Composition: Sodium chloride Sodium Phosphate Monobasic* Sodium Phosphate Dibasic*	15 ml 9 mg/ml 0,717 mg/ml 0,023 mg/ml	Solvent	 Ph.Eur. In house

* Produced at Hospital's Pharmacy

2.1.P.2 Pharmaceutical Development

See section 2.1.S.2.2

2.1.P.3 Manufacture

VU University Medical Center
Dept of Nuclear Medicine & PET Research
De Boelelaan 1107
1081 HV Amsterdam
The Netherlands
(Holder manufacturing license)

After the on column reaction the solid phase extraction columns are washed with sterile ethanol and water for injection. The ^{18}F-Fluormethylcholine is then extracted from the column with 5 ml 0,9 % sodiumchloride and collected in a sterile vial which already contains 10 ml sterile phosphate buffer.
The thus formulated ^{18}F-Fluormethylcholine is filter sterilized using a dispensing set (see figure 4) through a sterile 0,22 µm Millex GV filter with helium gas as driving force.
The result of the filtration/dispensing is 3 separate vials: one is used for the quality control of drug product for release purposes, one vial is kept to analyse on sterility, while the third vial is transferred to the hotlab for the patient delivery. (After release)
Equipment used during filtration process are sterile needles, tubing and couplers, pre-sterilized vials and Millex GV filters. Using aseptic assembly techniques within a class A work area, all materials are connected to a closed system as shown in figure 4.

When the ^{18}F-Fluormethylcholine is shipped to an external hospital the product and analysis vial are sterilized by autoclavation (6 min 134°C, 3 bar). During the first performed product validation (12-2008) it was shown that the autoclavation procedure did not had any effect on the radiochemical purity.

2.1.P.4 Control of Excipients

2.1.P.4.1 Specifications

See section 2.1.P.5.1

2.1.P.4.2 Analytical Procedures

See section 2.1.P.5.2

2.1.P.4.3 Validation of Analytical procedures

See section 2.1.P.5.3

2.1.P.4.4 Justification of Specifications

See section 2.1.P.5.6

2.1.P.4.5 Excipients of Human or Animal Origin

Not applicable.

2.1.P.4.6 Novel Excipients

Not applicable.

2.1.P.5 Control of DRUG Product

2.1.P.5.1 Specifications (s)

Clinical trial batches of [18F]Fluoromethylcholine will meet the following specifications:

Table 3: Quality specification for [18F]Fluoromethylcholine

Description	Requirements	Method
Appearance	Clear and colourless solution	Visual inspection
pH	4 - 8	Measurement with electronic pH-electrode
Radiochemical purity (HPLC)	≥ 95 %	HPLC
Radiochemical identity	Rt = 5 - 7 min (HPLC)	
Chemical purity	Besides injection peak in UV no other peaks in QC-HPLC according to reference chromatogram.	
Integrity filter	Pressure test filter > 2 bar	Filter is tested on integrity
Aceton*	≤ 50 ppm	Residuals determined with internal standard on a GC
Acetonitril*	≤ 50 ppm	
Dibromomethane	≤ 50 ppm	
2-(Dimethylamino)-ethanol	≤ 1000 ppm	
Ethanol concentration*	≤ 2 %	
Sterility**	Sterile	Sterility test
Bacterial endotoxin content	Sample value ≤ 2.5 EU/ml (Vmax = 70 ml)	Performed on endosafe PTS (Charles River)

* test not part of release testing but part of validation process
** test results available only two weeks after production

2.1.P.5.2 Analytical Procedures

The panel of analytical tests includes: visual inspection, pH, (radio)chemical purity (HPLC), residual solvent analysis, filter integrity test, bacterial endotoxin content and sterility.
Full end-product testing will be performed on all batches of ^{18}F-Fluoromethylcholine manufactured for human use. With the exception of the tests for residuals solvents (acetone, acetonitrile and ethanol), and sterility, all quality control tests will be completed prior to release of the final drug product for administration.

Appearance
Visual inspection is performed after final sterile filtration to confirm that the solution is clear and colorless.

pH
The pH of the drug product is determined by pH electrode.

(Radio)chemical purity, specific activity
The HPLC system consists of the following components and parameters:
Column: Waters XTerra MS C18 5 µm 150 * 3.9 mm column
Mobile phase: 10 mM sodiumheptanesulphonic acid, 10 mM sodiumazide / Acetonitril 95 / 5
Run time: 10 minutes
Flow: 1.0 mL/min
1 µL of the QC sample is injected on HPLC for analysis.
^{18}F-Fluoromethylcholine will elute from the column at 5 – 7 min.

Determination of endotoxin content
Endotoxin levels are assessed by use of an FDA-licensed LAL test system according to the instructions provided by the supplier (Endosafe®-PTS, Charles River).

Filter Integrity Testing
The filter integrity test is performed according to the bubble-point method, according to Eur. Pharmacopeia. The integrity of the sterile end filter is tested as part of the manufacturing process.

Sterility
Monitoring of the aseptic processing conditions is done by sending the sterility sample of the dispensing set to Dep. of medical microbiology of Vumc, after decay. The test is done as a post-release test.

Residual solvent analysis
Concentrations of dibromomethane and dimethylaminoethanol are quantified by FID-gas chromatography by use of internal standard and pre-run calibration curves, as a release parameter of every single production. The remaining residual solvents acetone, acetonitrile and ethanol are done as a post-release test, and performed from every validation run and every 10th production thereafter.

2.1.P.5.3 Validation of Analytical Procedures

The analytical procedures are validated and adequate to detect significant deviations from the specifications.

2.1.P.5.4 Batch Analyses

Three consecutive batches of [18F]Fluoromethylcholine were produced in which the quality of the formulated product will be validated against the release and non-release requirements, before the production process will be approved by the QP. Only after approval the product will be produced for human application.

2.1.P.5.5 Characterization of Impurities

Radiochemical impurities, as detected by radio-HPLC will be less then 2 %, while non-radioactive impurities will not be present as detected by HPLC-UV.

2.1.P.5.6 Justification of Specification(s)

Radiochemical purity
The Radiochemical Purity limit (> 98 %) is well above the range of other (marketed) radiopharmaceutical products and reasonably achievable.
Other specifications
Appearance, pH, integrity filter, endotoxine content and residuals solvents are set as to be expected values for this manufacturing method, within the range of other (marketed) radiopharmaceutical products and reasonably achievable.

2.1.P.6 Reference standards

See section 2.1.S.5.

2.1.P.7 Container Closure System

The container/closure system used for [18F]Fluoromethylcholine Injection is purchased from qualified vendors and consists of empty sterile vials, sterile needles, sterile tubing with long needles and sterile 0,2 µm millex GV filters. Using aseptic assembly techniques within a class A work area, sterile needles are attached to the millex GV filters. All needles, tubings and vials are connected to a closed system as shown in figure 3.

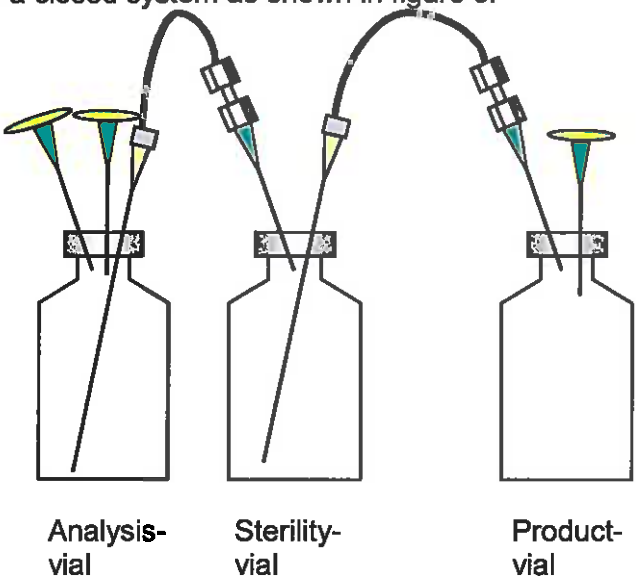

Figure 4: Completed Container/Closure Assembly for [18F]fluoromethylcholine Injection

The membrane sterilizing filter, and venting filter are manufactured by Millipore Corporation.
The aseptically assembled container/closure system is transferred to the hot cell and the inlet port of the sterilizing filter attached to the product outlet line that delivers the formulated product of [18F]fluoromethylcholine.

2.1.P.8 Stability

Half-life of [^{18}F]Fluoromethylcholine is 110 min. Injection takes place immediately after production, for patient studies at VUmc. However, the stability of the product has been investigated nonetheless and results were that the product is stable for at least 6 hours after production. This allows the product to be shipped to external hospitals.

2.2. Non-clinical pharmacology, pharmacokinetics and toxicology

Radiolabeled choline analogues, including [11C]choline and [18F]methylcholine, are radiopharmaceutical drugs which are already clinically used for many years in several clinical hospitals, the department of Nuclear Medicine & PET Research of the VU Medical Center Amsterdam included.

While phosphorylcholine is present at low levels in normal tissues, this enzyme reaches a high content in most cancers. Phosphorylcholine is the first intermediate in the stepwise incorporation of choline into phospholipids, by means of an active mechanism [Hara, 2002 (1)]. Choline is a body-own substance and is necessary for the normal function of the mammalian organism. In the human body, choline is needed for the synthesis of phospholipids in cell membranes, methyl metabolism, transmembrane signaling, and lipid-cholesterol transport and metabolism. Intracellular choline is rapidly metabolized to phosphorylcholine (PC); it may also undergo acetylation to form acetylcholine or oxidation to form betaine (mainly in liver and kidney). The phosphorylation is catalyzed by the enzyme choline kinase. Once phosphorylated, the polar PC molecule is trapped within the cell [Schöder, 2004 (2)].

The biologic basis for radiolabeled choline uptake in tumors is the malignancy induced upregulation of choline kinase, which leads to the incorporation and trapping of choline in the form of phosphatidylcholine (lecithin) in the tumor cell membrane [Jadvar, 2011 (3)]. Various published studies have revealed an increased choline uptake as well as an upregulated activity of choline kinase and elevated levels of PC in cancer cells [Ratman,1995 (4); Ackerstaff, 2001 (5); Katz-Brull, (6)]. For more data on the function of choline and the alterations in choline metabolism, see [(7)-(13)].

Based on the increased choline uptake in tumor cells, [11C]choline was developed and used as a PET tracer for cancer visualization, such as brain tumor, lung cancer, esophageal cancer, colon cancer, bladder cancer, prostate cancer and other cancer types. [18F]-labeled choline analog has also been synthesized and investigated, the superior 18F labeling being justified on grounds of longer half-life (109 minutes versus 20 minutes in the case of 11C) and the shorter positron range [DeGrado, 2001 (13); Hara, 2002 (1)] .

The biodistribution of [18F]-labeled is very similar to that of choline except for the very rapid urinary excretion. For this reason, [18F]-radiolabeled choline is extremely feasible to reflect pharmacological behaviour of choline itself. The efficacy of radiolabeled choline for localizing primary or metastatic prostate cancer has now been studied extensively [(14)-(19)]. [11C]choline blood clearance is very rapid (approximately 7 min), with the largest share of tracer remaining trapped within cells, with rapid uptake in prostate tissue (38). This allows for imaging as early as 3 to 5 min after tracer injection and provides images of good diagnostic quality [Hara, 2002 (8); Hara, 1998 (20)]. Physiologically increased tracer uptake is noted in salivary glands, lung, liver, kidneys and adrenal glands [Roivanen, 2000 (21)].).

Pharmacokinetics of [18F]fluormethylcholine in mice

A study conducted bij DeGrado et al [DeGrado, 2002 (10)] under a protocol approved by the Duke University Institutional Animal Care and Use Committee, evaluated the kinetics and radiation dosimetry of [18F]Fluoromethylcholine using murine and human biodistribution data. Tumor-bearing groups of mice were compared after subcutaneously being injected with human cancer cells (PC-3 androgen-independent prostate carcinoma or MCF7 estrogen receptor–positive breast carcinoma) with a control group consisting of 4- to 6-wk-old male athymic mice. The radiotracer uptake was measured, after injection of [18F]Fluoromethylcholine (0.74 –1.48 MBq [20–40 µCi]) in both these

groups, not before the tumor volume has reached at least 0.5 cm^3 in cancer-bearing mice. Organs and tissues were resected, after a prescribed period of time. The radioactivity of [18F]Fluoromethylcholine was measured by means of a γ-counter. The percentage of the injected dose in the urine was measured for the bladder.

The results of the biodistribution of [18F]Fluoromethylcholine in mice are shown in the table below:

Uptake (% Dose kg/100 g) of 18F-FCH in Tissues of Tumor-Bearing and Control Mice (male BALB/c *nu/nu*)

	PC-3			MCF7	Control	
Tissue	10 min (*n* = 5)	30 min (*n* = 3)	60 min (*n* = 5)	60 min (*n* = 5)	60 min (*n* = 5)	10 h (*n* = 6)
Tumor	3.6 ± 0.6	7.1 ± 2.1	7.9 ± 5.0	4.3 ± 1.5	—	—
Blood	2.7 ± 0.9	3.3 ± 0.2	1.5 ± 0.6	2.3 ± 0.5	1.1 ± 0.3	1.5 ± 0.4
Heart	15.5 ± 5.9	13.2 ± 2.6	12.7 ± 3.2	17.2 ± 2.5	18.0 ± 8.0	23.5 ± 5.1
Brain	0.8 ± 0.3	1.0 ± 0.2	0.8 ± 0.1	1.3 ± 0.4	1.4 ± 0.6	1.7 ± 0.4
Lung	18.0 ± 5.3	17.1 ± 1.4	21 ± 4.4	22.5 ± 2.8	30.2 ± 10.9	28.6 ± 5.8
Liver	50.7 ± 15.3	56.7 ± 13.2	58.4 ± 40.6	37.8 ± 13.0	24.5 ± 13.4	26.6 ± 9.8
Kidney	127.7 ± 27.6	116 ± 17.0	94.3 ± 31.0	99.2 ± 25.4	75.6 ± 25.7	90.6 ± 17.5
Skeletal muscle	4.4 ± 1.8	1.1 ± 1.0	4.1 ± 0.6	4.1 ± 0.9	2.2 ± 1.0	2.9 ± 1.0

The kidney and liver were the primary sites of uptake for [18F]Fluoromethylcholine, similar to previous findings with radiolabeled choline [Hara, 1997 (8)] and [Haubrich, 1975 (22)].

There were no differences found in biodistribution patterns between the normal tissues of the control and the tumor-bearing groups of mice at 1 h after administration. Furthermore, no significant difference was found in the biodistribution of [18F]Fluoromethylcholine between the 2 groups of mice bearing breast and prostate cancer xenografts.
In the prostate cancer xenograft model, the kinetics were observed to be rapid and the distribution in the tissues was essentially static after 10 min, while no significant differences in the biodistribution of [18F]Fluoromethylcholine between 1 and 10 h after administration were found in the control group. TheseThis phenomena suggested the efficient metabolic sequestration of the radiotracer in tissues consistent with previously observed lipid incorporation of the radiolabel [DeGrado, 2001 (13)].

Pharmacokinetics of [18F]Fluoromethylcholine in human subjects

The biodistribution of [18F]Fluoromethylcholine was investigated in 7 male patients with prostate cancer and 5 female patients with breast cancer within the same study conducted bij DeGrado et al (10). The patients were asked to refrain from food 4 hours prior to the injection of 110–220 MBq [3–6 mCi] [18F]Fluoromethylcholine. A Whole-body emission PET scan, followed by a transmission scan, was performed for every patient 10–20 min after administration of the radiotracer.

In the 5 female patients with breast cancer, a dynamic PET scan was performed over the heart in the first 10 min after injection in order to obtain time–activity curves of radioactivity in the left ventricular blood pool. The concentration of radioactivity in various tissues was calculated by manually drawing regions of interest on the PET images. Data for radiation dosimetry were collected by determining the amount of radioactivity distributed to the whole organ, namely in liver, kidneys, spleen, and urinary bladder.

Using the image-derived blood radioactivity concentration as previously described [Gambhir, 1989 (2324)], the pharmacokinetics were fitted to a model that had 2 rapid exponential components plus a constant. The two rapid phases, which were nearly complete by 3 min after administration, represented 93% of the peak radioactivity concentration. Thus, the tracer is extensively cleared in the first 5 min after administration. The concentration of 18F radioactivity in liver increased rapidly in

the first 10 min and then increased slowly thereafter. The concentration of ^{18}F radioactivity in lung was relatively low at all times.

The results of the biodistribution of [^{18}F]Fluoromethylcholine in human subjects at 10–55 minutes after injection are presented in the table below. The biodistribution in humans is very similar to that in mouse with the exception of the lower lung and myocardial uptake in humans. The highest uptake was in the kidney followed by the liver and spleen. The mean activity in the bladder was 4.9% of the injected dose for females and 1.9% of the injected dose for males, although the difference was not statistically significant.

Parameter	Female	Male
Subjects		
n	5	7
Age (y)	44 ± 7	74 ± 8
Body weight (kg)	70.8 ± 22.6	81.4 ± 14.0
Tissue (% dose/g × 10^3)		
Myocardium	2.52 ± 1.06	1.65 ± 0.51
Blood	1.62 ± 0.77	0.84 ± 0.28
Skin	0.36 ± 0.12	0.32 ± 0.08
Skeletal muscle	0.70 ± 0.27	0.66 ± 0.27
Lung	1.25 ± 0.44	1.36 ± 1.21
Normal breast	0.91 ± 0.37	—
Liver	13.52 ± 4.69	9.42 ± 1.90
Renal cortex	24.70 ± 13.85	14.95 ± 6.06
Intestine	2.22 ± 1.12	1.46 ± 0.85
Thyroid	2.83 ± 1.12	1.70 ± 0.38
Salivary gland	6.23 ± 3.26	3.47 ± 1.52
Spleen	7.84 ± 2.61	5.54 ± 2.46
Normal bone	1.17 ± 0.58	0.70 ± 0.23
Urine	6.34 ± 2.50	8.88 ± 4.36
Organ (% dose/organ)		
Spleen	2.97 ± 3.46	1.35 ± 0.75
Liver	14.21 ± 0.84	13.71 ± 2.63
Left kidney	4.68 ± 1.44	4.48 ± 3.34
Right kidney	4.44 ± 1.25	3.70 ± 1.90
Urinary bladder	4.88 ± 4.79	1.88 ± 1.58

Radiation Dosimetry Estimates

The table below illustrates the estimated radiation doses for humans in mSv/MBq (rad/mCi) administered, with the doses derived from mouse data shown for comparison.

	Murine data (dose per unit activity)		Human data (dose per unit activity)			
			Female		Male	
Organ or tissue	mSv/MBq × 10^2	rad/mCi	mSv/MBq × 10^2	rad/mCi	mSv/MBq × 10^2	rad/mCi
Myocardium	1.24	0.046	1.74 ± 0.31	0.064 ± 0.011	1.48 ± 0.32	0.048 ± 0.006
Spleen	—	—	6.37 ± 1.94	0.236 ± 0.072	5.42 ± 2.13	0.175 ± 0.079
Small intestine	—	—	2.57 ± 0.56	0.095 ± 0.021	2.30 ± 0.56	0.078 ± 0.019
Uterus	—	—	1.99 ± 0.35	0.074 ± 0.013	—	—
Thyroid	—	—	1.48 ± 0.34	0.055 ± 0.012	1.38 ± 0.25	0.049 ± 0.006
Breast	—	—	0.98 ± 0.22	0.036 ± 0.008	—	—
Lung	1.16	0.043	1.29 ± 0.15	0.048 ± 0.005	1.14 ± 0.28	0.038 ± 0.011
Liver	8.11	0.300	6.94 ± 0.41	0.257 ± 0.015	5.90 ± 1.15	0.191 ± 0.032
Kidney	21.90	0.810	17.35 ± 4.82	0.642 ± 0.178	15.86 ± 7.21	0.547 ± 0.324
Bone	1.03	0.038	2.18 ± 0.32	0.081 ± 0.012	1.91 ± 0.35	0.064 ± 0.008
Muscle	0.90	0.032	1.23 ± 0.14	0.046 ± 0.005	1.10 ± 0.18	0.037 ± 0.005
Red marrow	1.16	0.043	2.02 ± 0.18	0.075 ± 0.007	1.74 ± 0.28	0.057 ± 0.004
Testes	0.76	0.028	—	—	1.36 ± 0.41	0.039 ± 0.004
Ovaries	1.05	0.039	1.80 ± 0.15	0.067 ± 0.006	—	—
Bladder wall	1.32	0.049	9.66 ± 8.63	0.358 ± 0.319	6.32 ± 5.97	0.123 ± 0.075
Effective dose equivalent	2.97	0.110	3.69 ± 0.59	0.137 ± 0.022	3.13 ± 0.73	0.101 ± 0.020

The authors of the study concluded that the dose-critical organ is the kidney, which receives 0.17 and 0.16 mSv/MBq (0.64 and 0.55 rad/mCi) for females and males, respectively. To comply with the 0.05-Sv single-organ dose per study limit established by the Food and Drug Administration (FDA) for research subjects, it is required that the administered activity of [^{18}F]Fluoromethylcholine be limited to 4.07 MBq/kg (0.110 mCi/kg) for women and 4.14 MBq/kg (0.112 mCi/kg) for men. The effective dose equivalent for humans from administration of 4.07 MBq/kg (0.110 mCi/kg) is approximately 0.01 Sv for females and males, which is below the single-study FDA limit of 0.03 Sv for research subjects.

2.3 CLINICAL DATA

[^{18}F]Fluoromethylcholine has been used for several years in PET imaging studies in humans. The most applications of this radiotracer are related to urological malignancies. Clinical studies have shown the role of choline at initial diagnosis, staging and restaging of prostate cancer patients [Husarik, 2008 (24); Rioja, 2009 (25)]. In case of biochemical Prostate Specific Antigen (PSA) relapse, restaging of the disease for the detection of lymph node and distant recurrence it can be used as first diagnostic procedure, enabling the clinician to choose the best treatment option [Fuccio, 2010 (26)].
[^{18}F]Fluoromethylcholine also appears to be a useful PET/CT tracer for the detection and surveillance of Hepatocellular Carcinoma, having a higher sensitivity then [^{18}F]FDG, especially in well-differentiated forms [Talbot, 2010 (27)]. This lipid analogue for PET imaging has also shown good diagnostic performances for the detection of well-differentiated adenocarcinoma or bronchoalveolar carcinoma, being able to detect all malignant lesions with at least a 2.0 cm short axis [Balogova, 2010 (28)]. In brain imaging, [^{18}F]Fluoromethylcholine was proved to be useful in the detection of recurrent tumours, by excellent delineation of the tumor from normal brain [Kwee, 2007 (29)].

For more clinical results **please** refer to Pubmed for published clinical studies (^{18}F and choline/clinical studies, **28** hits).

2.3.1 CLINICAL PHARMACOLOGY

For information on blood metabolism of [18F]Fluoromethylcholine during PET imaging in humans, please refer to "[^{18}F]Fluoromethyl-[1,2-sH4]-choline: a novel radiotracer for imaging choline metabolism in tumors by positron emission tomography", [Leyton, 2009 (30)].

2.3.2 CLINICAL PHARMACOKINETICS

In terms of pharmacokinetics, limited data in patients with suspicion of metastases due to biochemical PSA recurrence was published. In a study described by Uusijarvi et al [Uusijarvi , 2010 (8 32)] four patients with radical prostatectomy in history were injected with [^{18}F]Fluoromethylcholine. Whole-body PET/CT images were performed 60 minutes after injection. Blood samples were taken and all urine was collected for 3.5 h. The activity concentrations [Bq ml^{-1}] in the liver, kidneys, spleen, salivary glands and tumours were achieved from the PET images. Regions of interest (ROIs) were drawn within the organs and tumours and a mean value was calculated. The activity content in an organ was expressed as percent injected activity (%IA). The highest activity concentration was found in kidneys (43 kBq ml(-1). The organ with highest activity content was the liver (11 % of injected activity, % IA). Thirty minutes after the injection 4-16 % IA was left in the blood and less than 9 % IA was excreted with the urine during the first 3.5 h after injection.
These results are consistent with those publicated by DeGrado [DeGrado, 2002 (31)] and which were in detail described in section 2.2.
For more information, please refer to Pubmed for published clinical studies on pharmacokinetics (^{18}F and choline/pharmacokinetics, 18 hits).

2.3.3 HUMAN EXPOSURE

[^{18}F]Fluoromethylcholine has been investigated by many rearchers all over the world, including VU University Medical Center, and in many patients. Please refer to sections 2.2 and 2.3 and the references mentioned at the end of this IMPD (2.4).

2.4 LIST OF STUDIES CONDUCTED & REFERENCES

A Summary of published manuscripts reporting [^{18}F]Fluoromethylcholine imaging studies

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2.5 Appendices

Appendix a: Production sheet of manufacturing [^{18}F]Fluormethylcholine (in Dutch)
Appendix b: Certificate of analysis precursor
Appendix c: Validation report Fluormethylcholine