Technetium nuclear medicine

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II Letnia Szkoła Energetyki i Chemii Jądrowej

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Technetium nuclear medicine

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Medical institute REAVIZ

Nuclear medicine – one of the axes of peaceful usage of nuclear energy

- Supervised by IAEA seeking :

- to promote the peaceful use of nuclear energy
- while inhibiting its use for any military purpose, including nuclear weapons

- Nuclear safety (U-235 less 20%)
- Exclusion of dirty bombs

- Allied to nuclear industry (R**adioisotope production**)

- Dealing with **Radioisotope use** – radiodiagnostics and radiotherapy

Nuclear medicine

Radiodiagnostic advantage

Nuclear medicine tests differ from most other imaging modalities in that diagnostic tests primarily show the ***physiological function* of the system being investigated** as opposed to traditional anatomical imaging such as CT or MRI.

- Radiotherapy
- **Radiation use for metastases treatment, etc.**

The most intensively used radioisotope is Technetium-99m

YOUTUBE: http://www.youtube.com/watch?v=v_8xM-mLxJ8

http://www.youtube.com/watch?v=c716Sj1HYVE

Tc-99m nuclear medicine

Practical concerns in nuclear imaging

- Although the risks of low-level radiation exposures are not well understood, a cautious approach has been universally adopted that all human radiation exposures should be kept **As Low As Reasonably Practicable**, "ALARP".
- The radiation dose from nuclear medicine imaging varies greatly depending on the type of study.

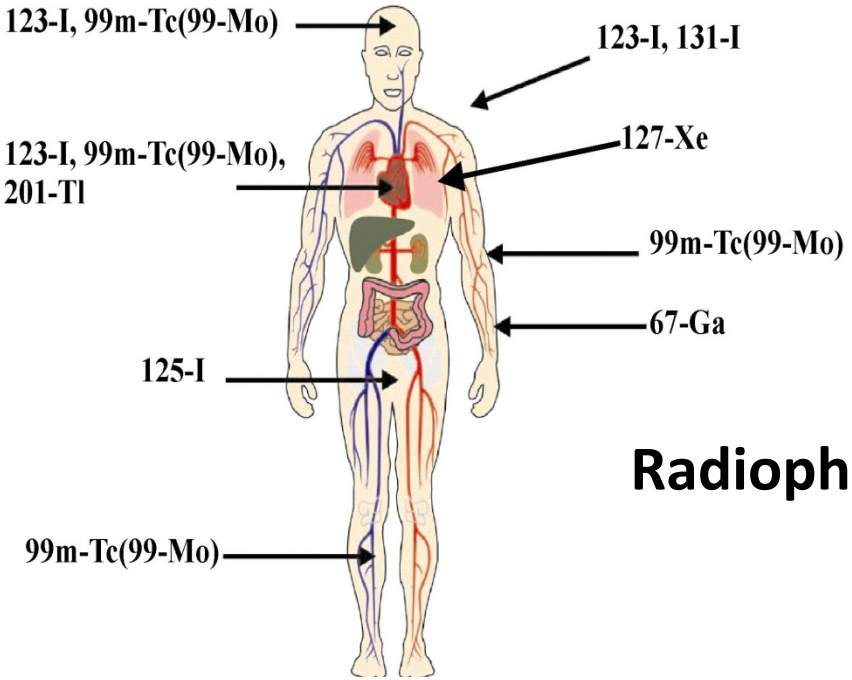
Tc-99m

- **Among many radionuclides that were considered for medical-use, none were as important as the Technetium-99m.**
- **Discovered in 1937 by C. Perrier and E. Segre as an artificial element, it filled an empty space number 43 in the Periodic Table.**
- **The development of a Mo-99-Tc-99m generator system in the 1960s became a practical method for medical use.**
- **Today, Technetium-99m is the most utilized element in nuclear medicine and is employed in a wide variety of nuclear medicine imaging studies.**
- **The reason : its ideal nuclear and chemical properties**

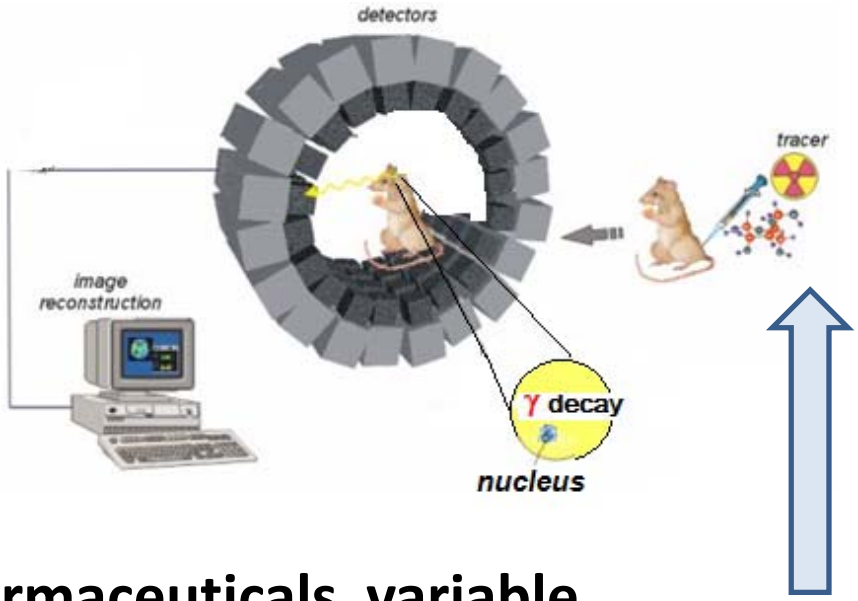
SPECT methodology and Tc-99m

Single Photon Emission Computerized Tomography

Radionuclides and tissues



Apparatus



Radiopharmaceuticals variable

SPECT tomograph

- Generator methodology :
- no Mo-99 is injected, just Tc-99m

From medical point of view Tc-SPECT

Clinically Important because :

- **Early diagnostics of complicated diseases.**
- ***Estimation of physiological function activity* of a local biosystem and its resistance both in pathological states and in normal biological states.**
- **Early diagnostics of metastases release and generalization in oncology.**
- **Rapid indices of the efficiency of medical, drug, X-ray or chemotherapy enabling the early choice of the most efficient method for the case.**

Tc-99m

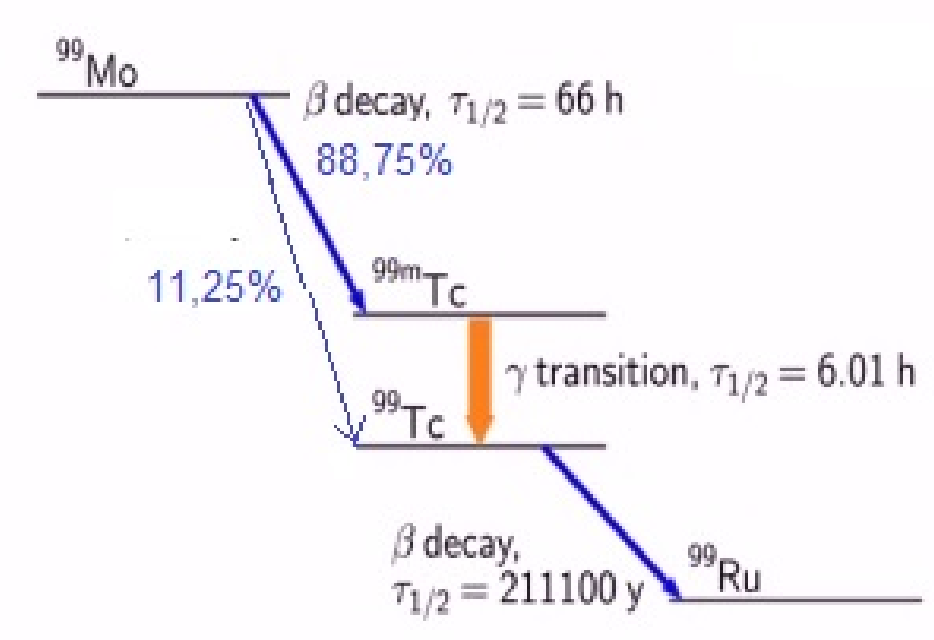
- Is it harmful?

- ALARP-efficient.
- Time comfortable
- Target tissue variable
- Bi-functionality loyal

Tc-99m Radionuclide properties for in Nuclear Medicine

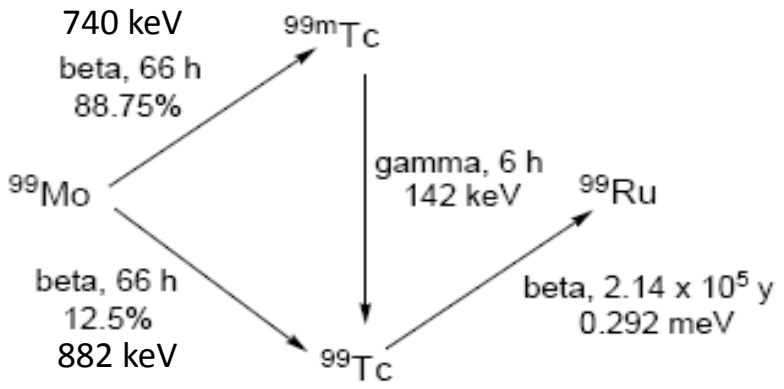
Nuclear diagnostics SPECT (single photon emission computer tomography)
requirements: gamma emitters 100-200 keV, $T_{1/2}$ = hours-days

- **Tc^{99m} nuclear isotope is used for medical imaging in 90% of cases all over the world due to its near ideal nuclear characteristics of a 6 h halflife and γ-ray emission energy of 142 keV**



Why radionuclide generator?

- The ready availability of the isotope using the $^{99}Mo/^{99m}Tc$ generator developed in Brookhaven in the early 1960s.

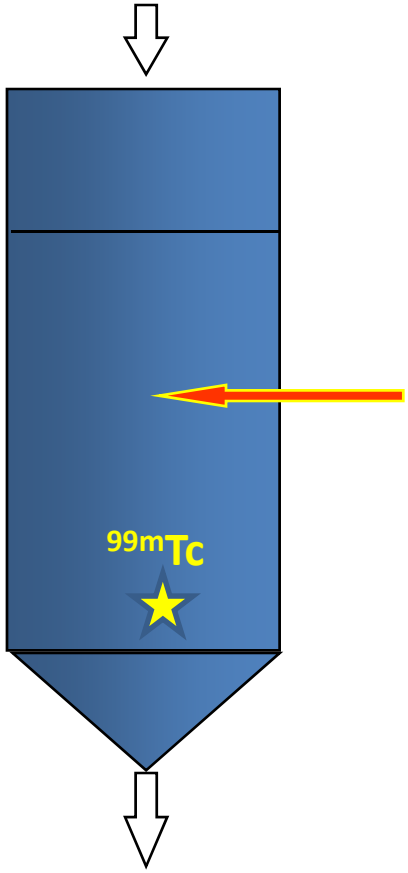


- The first generator consisted of $[^{99}MoO_4]^{2-}$ absorbed at the top of an alumina ion exchange column.
- The radionuclide ^{99}Mo decays continuously to **^{99m}Tc** which can be periodically and preferentially eluted with physiological saline solution (0.15 m NaCl) over a period of 7–10 days.

- Therefore the supply of Tc-99m generators strongly depends on the ability ***to produce Mo-99***. *Somebody says it is* ***a by-product of nuclear industry. No, it is the special target product ^{235}U (n,f) [^{99}Mo + ^{136}Sn + n] !***
- *We never produce Tc-99m !*
- *We have no Tc-99m in the patient's body in 2-3 days after injection*
- **Multiple approaches for Mo-99 production exist:**
- Uranium-235 fission (**HEU** and **LEU**) – bonded to nuclear industry (reactor availibility)
- Mo-98 irradiation with neutrons
- Natural Mo irradiation with neutrons
- Cyclotron production etc.

Tc generator and kit

isotonic saline in

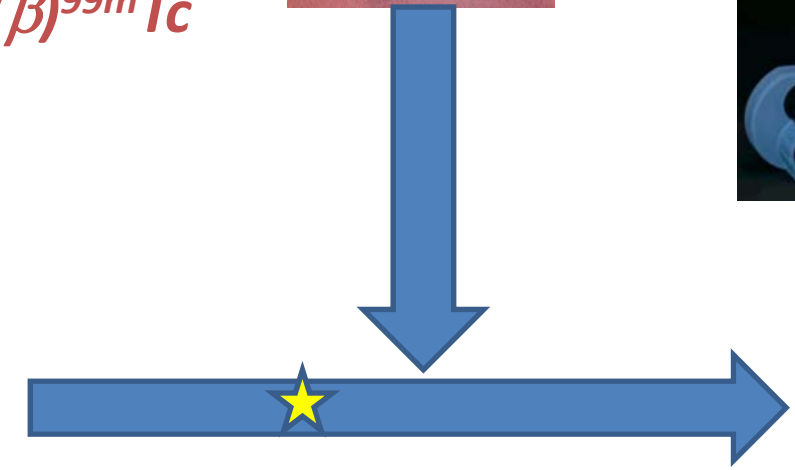


$[^{99}MoO_4]^{2-}$ on alumina support

^{99}Mo (β)^{99m}Tc

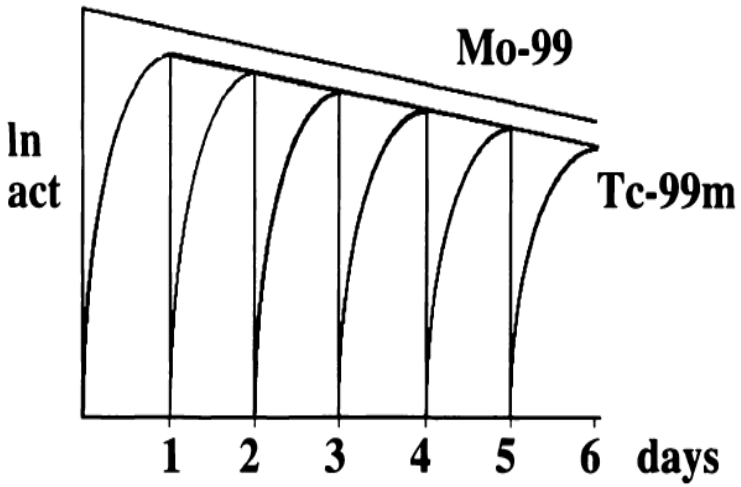
Modern Tc-99m Generator

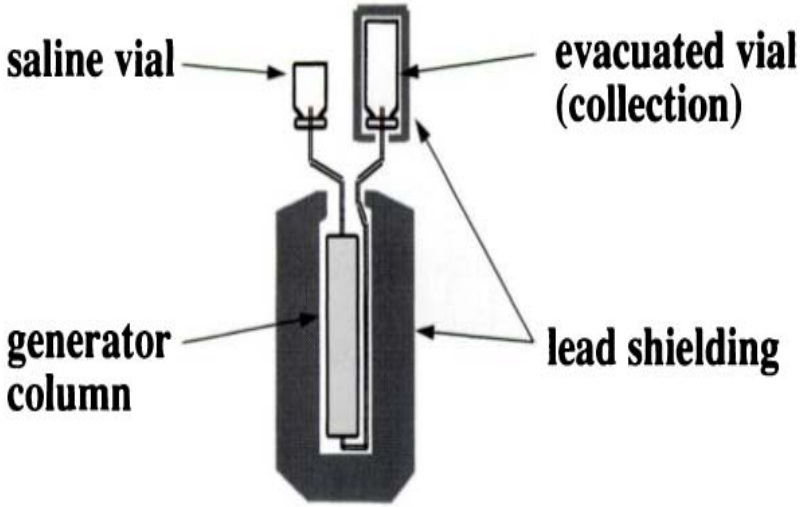
$[^{99m}TcO_4]^-$ + isotonic saline out ca 10^{-8}M



***Chromatographic**, extraction, sublimation generators were elaborated during the last decades*

Tc generator usage mode



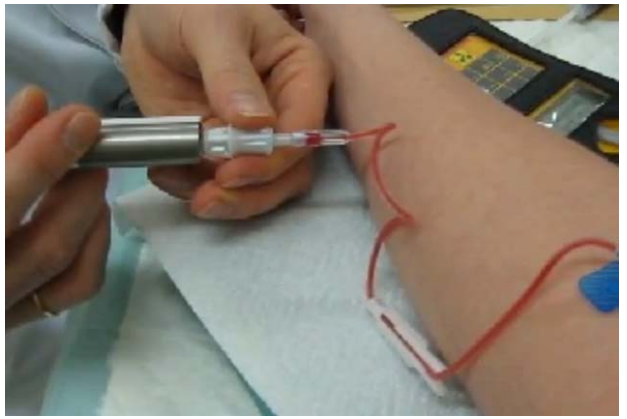


Tc-99m activity accumulation and stripping

Imaging techniques for technetium

- The saline pertechnetate eluate from the Mo^{99}-^{99m}Tc generator is introduced by syringe *via a septum into a vial containing the* reagents necessary to produce the imaging agent.
- After a suitable incubation period the radiopharmaceutical is injected into the patient, and after time for biodistribution to occur, the image data is collected by a gamma camera equipped with a NaI scintillation detector and photomultiplier system .
- The camera is rotated around the patient or a multidetector array is used to create a tomographic image by use of a sophisticated computerised program which reconstruct the image from a series of projections

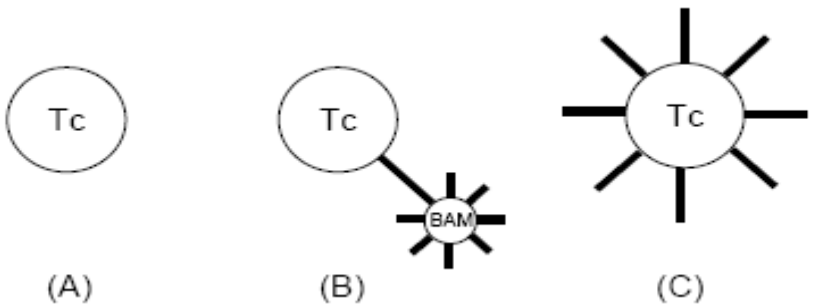
- A successful imaging agent (radiopharmaceutical kit) will generally direct 1–5% of the injected dose of activity to the target organ, the bulk of the remainder generally being excreted *via the kidneys.*



- *The total radiation dose from a Tc scan* is comparable with that from a conventional X-ray.

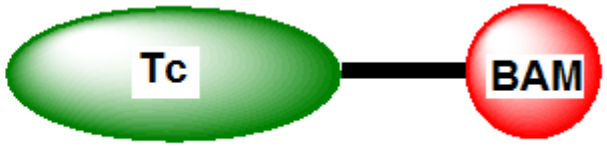
Types of technetium imaging agents

- Tc-99m application for imaging in 1961 involved the use of $[^{99m}TcO_4]^-$ for diagnosis of thyroid disease based on the principle that it behave similarly to ***iodide***, known to be taken up by the ***thyroid***.
- The biodistribution and targeting ability thus depended solely on the size, and charge of $[^{99m}TcO_4]^-$.



- 'Tc essential' or **1st generation agents (A)** have been deployed with great success to image organs such as the heart, the brain, the kidney and the liver.
- **2nd generation agents (B) -** the targeting capability resides in a biologically active molecule (BAM) covalently linked to an appropriate Tc complex (typically – peptide).
- **3rd generation agents (C) are under way**

Targeting Technetium-99m Type advantages



First generation

Intrinsic targeting, dependent on size, lipophilicity, redox, charge etc.

Metal complex has crucial role

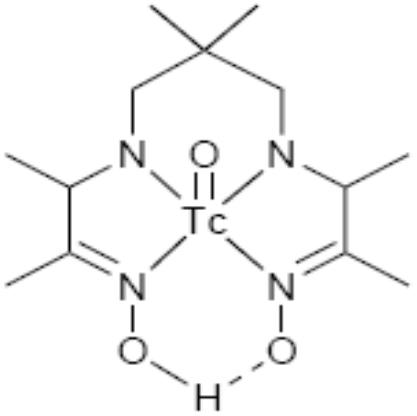
Second generation

Targeting via BAM attached to metal complex with high thermodynamic and kinetic stability

Metal complex may influence binding to receptor – modification of linker

1st generation Tc imaging agents

- ***Brain imaging***
- The principle demand to the agent that is to be accumulated in the brain is that it should be capable for traversing the blood–brain barrier (BBB).
- The complexe should be moderately lipophilic and not charged. In 1980s a series of neutral Tc-amine–oxime complexes we proposed to be prepared by reduction of [TcO4]- with SnCl2 in excess of the ligand.
- Amersham Intl. commercialized ***Ceretec*** agent utilising the HMPAO hexametazime which forms a neutral, square pyramidal TcV mono-oxo complex

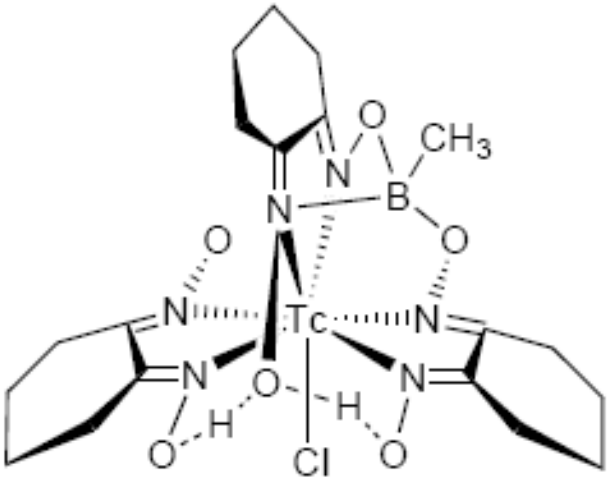


(A)

The Ceretec agent has limited stability and of Co2+ is now added to increase its lifetime.

1st generation Tc imaging agents

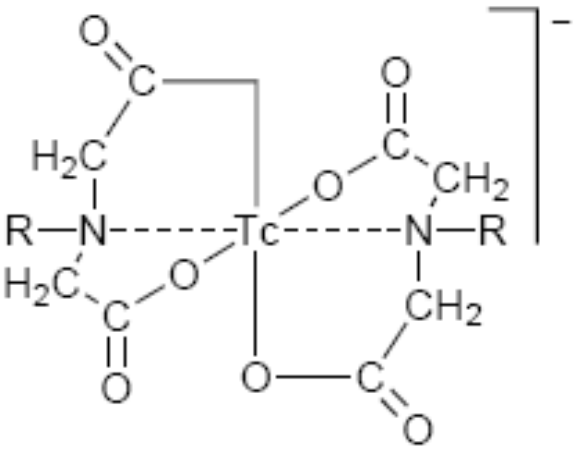
- ***Heart imaging***
- The first approved neutral myocardial perfusion agent is ^{99m}Tc-teboroxime (**Cardiotec**), which is a member of the BATO class of complexes, (BATO—boronic acid adducts of Tc dioximes).
- The complex has the formula [TcCl(CDO)(CDOH)2BMe], where CDOH2 = cyclohexane dione dioxime and is prepared by the reaction of $^{99m}TcO_4^-$ with a mixture of cyclohexane-1,2-dione dioxime and methyl boronic acid with SnCl2 as a reducing agent.
- 5 Min after injection 2.2% of the injected dose of this TcIII complex is found to accumulate in the heart *via a mechanism which is unknown* at this time,
- The complex exhibits rapid myocardial clearance in normal myocardium.

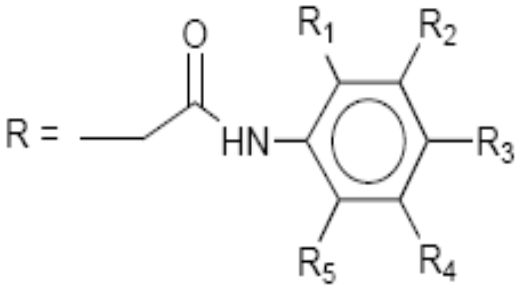


It is postulated that the neutral complexes may be washed out of the heart and it is the cationic complex which is subsequently retained.

1st generation Tc imaging agents

- ***Liver imaging***
- Technetium(III) complexes of HIDA [2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid] derivatives have been shown to be suitable for imaging the *hepatobiliary system (liver)*.
- Three ^{99m}Tc-HIDA analogues have been approved:
- ^{99m}Tc-Lidofenin **(TechneScan HIDA)**
- ^{99m}Tc-Mebrofenin **(Choletec)** and
- ^{99m}Tc-Disofenin **(Hepatolite)**.





Lidoferin $R_1 = CH_3$
Disoferin R_1 = isopropyl
Mebroferin $R_1 = R_3 = CH_3$, R_2 = Br

1st generation Tc imaging agents

- ***Liver imaging***
- ***Tc-sulfur colloid*** is also used for liver imaging and is believed to be made up of $^{99m}Tc_2S_7$ and colloidal sulfur.
- The Tc-sulfur colloid is produced by the sodium dithionite reduction of TcO_4^- in an acidic solution.
- 80–85% of the colloid is accumulated in the liver *via uptake in Kupffer cells by phagocytosis.*

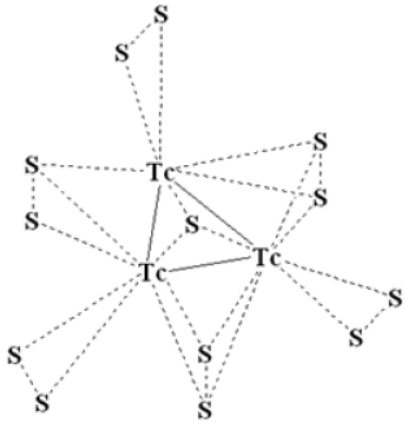


Fig.7. Structure unit fragment Tc_3S_{13} for technetium sulfide acc. to EXAFS studies[17]

(W. Lukens, J. Bucher, D. Shuh, N. Edelstein. *Environ. Sci. Technol.*, ***39 (2005) 8064***

-

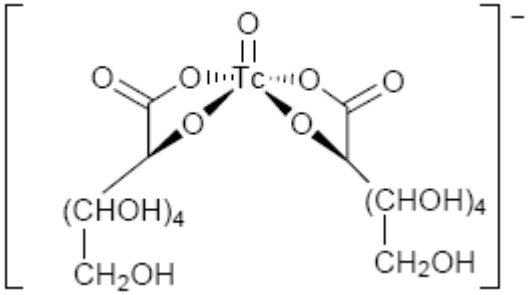
Mostly for environmental Tc)

It is difficult to believe that radiopharmaceutical Tc-S species are tri-nuclear

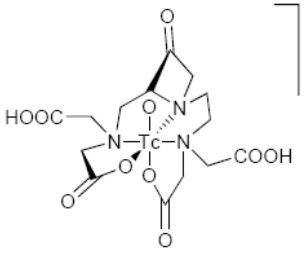
1st generation Tc imaging agents

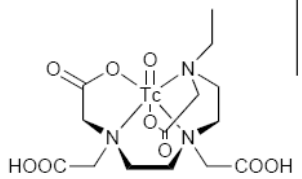
Kidney imaging

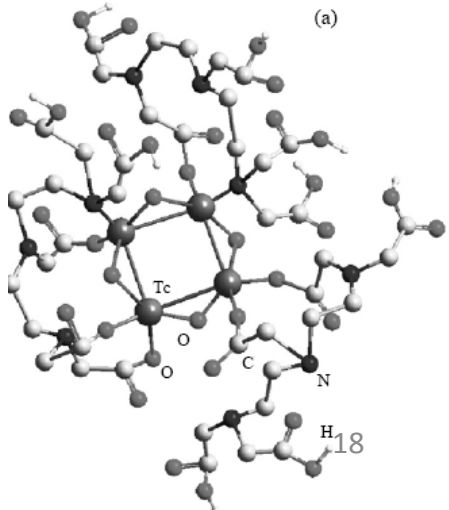
- [^{99m}TcO(glucoheptonate)$_2$]-, ***Glucoscan*** also known as ***TechneScan*** or ***Glucoheptate,*** is an early kidney imaging agent.
- The structure is unknown, believed to have the 5 coordinate Tc-structure
- *No more in use*

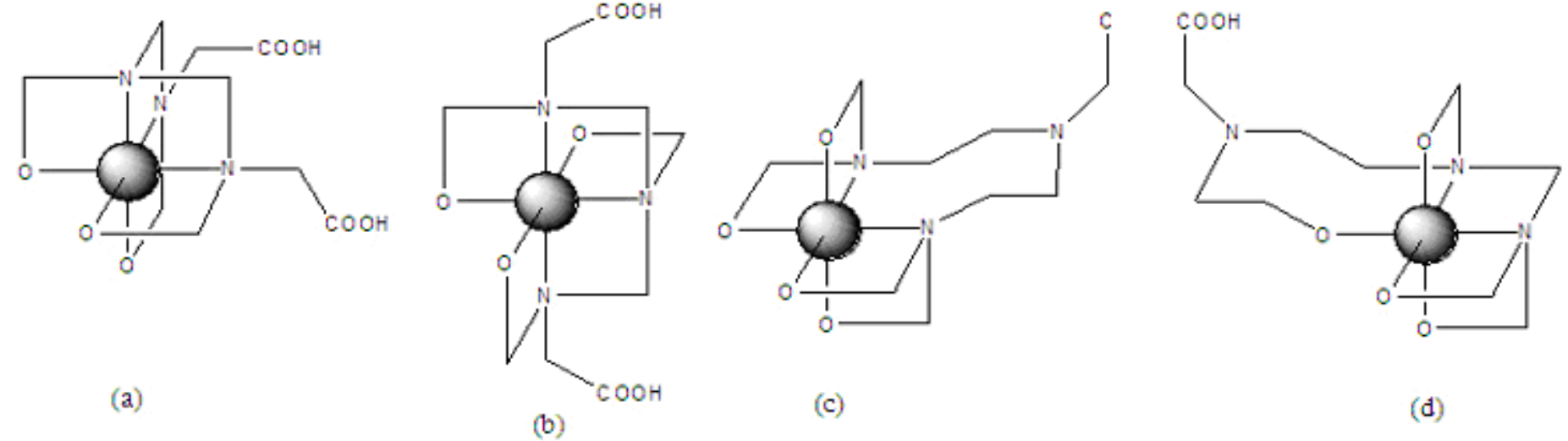


- ***^{99m}Tc-DTPA***, DTPA = diethylenetriaminepentaacetic acid, has approval for use as a kidney imaging agent.
- The ^{99}Tc analogue is shown by EXAFS to have polymeric structure. Contains Tc in both +IV & +V oxidation state.
- *It should differ*
- *from the KIT*









Tc-DTPA . . . M-DTPA

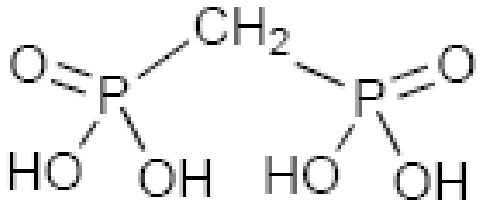
Me-DTPA

Спектр	Соединение	O–H	COOH	COOM	CH_2COOH	C–N
A	$H[Al(EDTA\text{-}5)(H_2O)]$	3400sh	1730sh	1650s	1230w	1097m
B	$H[Ga(EDTA\text{-}5)(H_2O)]$	3100sh	1740m	1650s	1233w	1100m
C	$H[In(EDTA\text{-}5)(H_2O)]$	3400sh	1690sh	1600s	1233w	1091s
D	$H[Tl(EDTA)(H_2O)]$	3440sh	...	1610s	1220m	1092s
					1244m	1116m
E	$H[Th(DTPA\text{-}8)]\cdot H_2O$	3300m	...	1600s	...	1085w
F	$H[Zr(DTPA)]\cdot 3H_2O$	3420sh	1725sh	1650s	...	1085w
G	$H_2[Fe(DTPA\text{-}6)]$	...	1730m	1650s	1218sh	1096w
H	$H_3[Ni(DTPA)]\cdot H_2O$	3190m	1735m	1602s	1235m	1100w
		3390m				
I	$H[Ni_2(DTPA\text{-}3,5)(H_2O)_4]\cdot 3H_2O$	3280s	...	1590s	...	1094w
J	$H_3[Cu(DTPA)]\cdot H_2O$	3330w	1765w	1605s	1210m	1088m
			1733m	1573s	1247w	
			1690sh			
K	$H[Cu_2(DTPA\text{-}3,4)(H_2O)]$	3410w	1732w	1597s	1210w	1116w
L	$H_3[Mo_2O_2(OH)_4(DTPA)]$	3310m	1724w	1630s	1230sh	1080w
M	$H_3[Mo_2O_2(OH)_3(TTHA)]\cdot 4H_2O$	3400m	1745w	1640s	1250sh	1075w

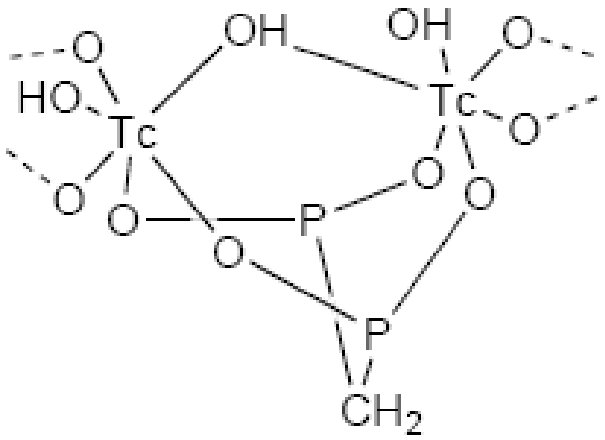
1st generation Tc imaging agents

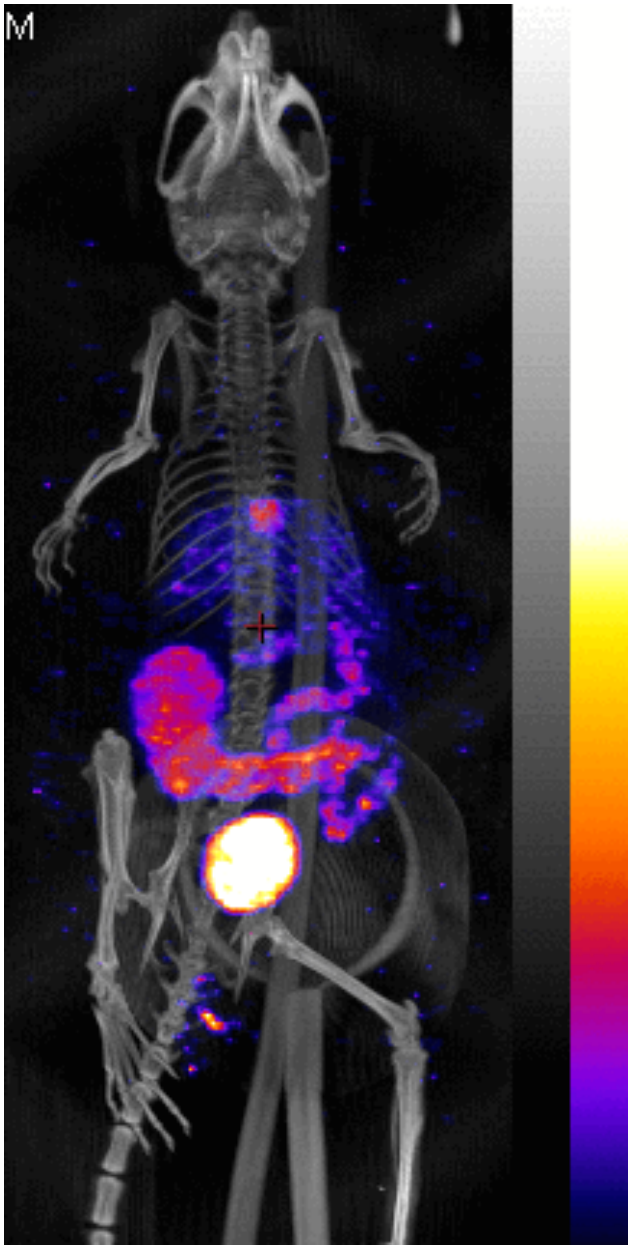
Bone imaging

- Tc-99-Diphosphonates such as methylenediphosphonate [MDP, show high performance as bone-imaging agents.
- The agent is prepared by reaction of the $[^{99m}TcO_4]^-$ generator eluate with MDP in the presence of $SnCl_2 \cdot 2H_2O$ as reductant



- At the ^{99}Tc level, reaction of $[^{99}TcBr_6]_2^-$ with H_4MDP led to the isolation and structural characterisation of a polymeric complex, so *no direct evidence for the RadPhPrep structure exists*





A SPECT/CT image of a 99m-Tc complex in a mouse

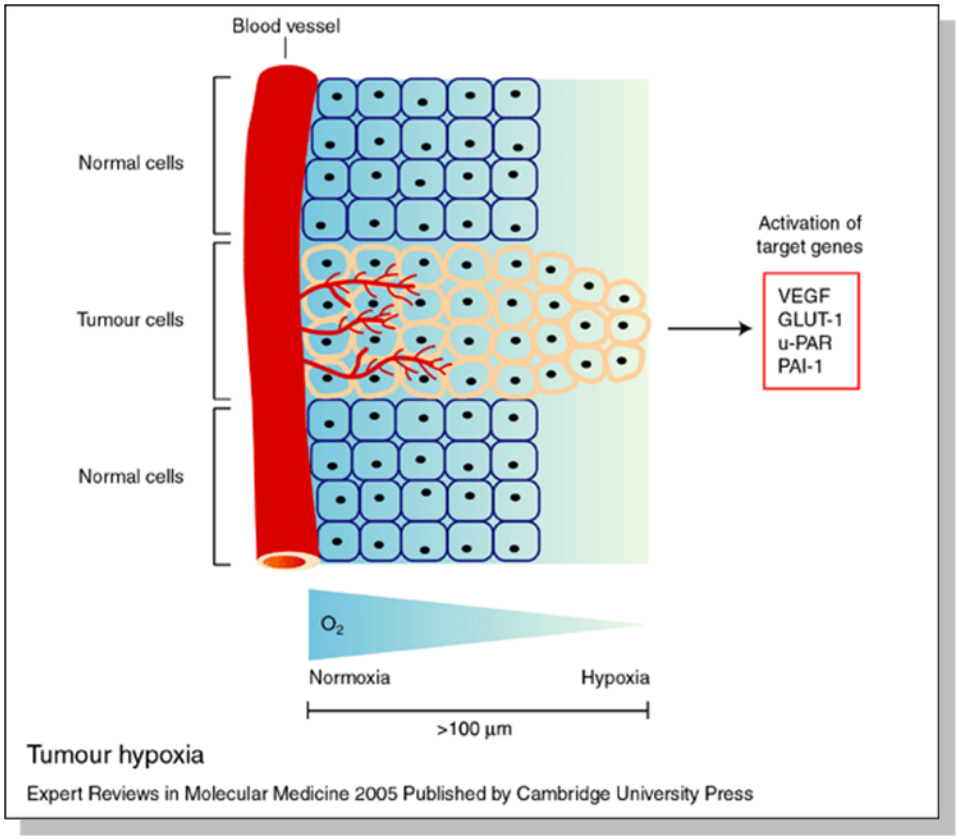
Prof R Muschel, E Bernhard and Dr S Smart, Gray Institute Oxford, 2008

Advantages of variability

- Widely variable oxidation state (0 to +7) with simple redox interconversion.
- Accessible from $[TcO_4]^-$ in aqueous media
- Variable coordination number (7 to 5) availabe
- Ready formation of multiple bonds to O and N which are stable in aqueous\saline media

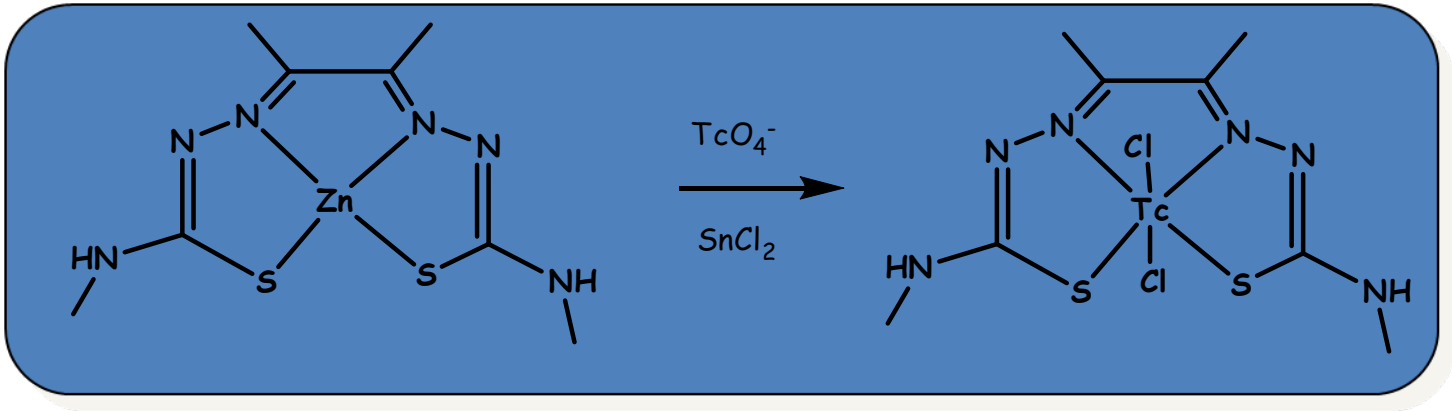
Thiosemicarbazone ligands and targeting hypoxia

Why are tumours hypoxic?



The hypoxic areas do not respond to radiotherapy. Essential to know extent of hypoxic zone for appropriate treatment regime

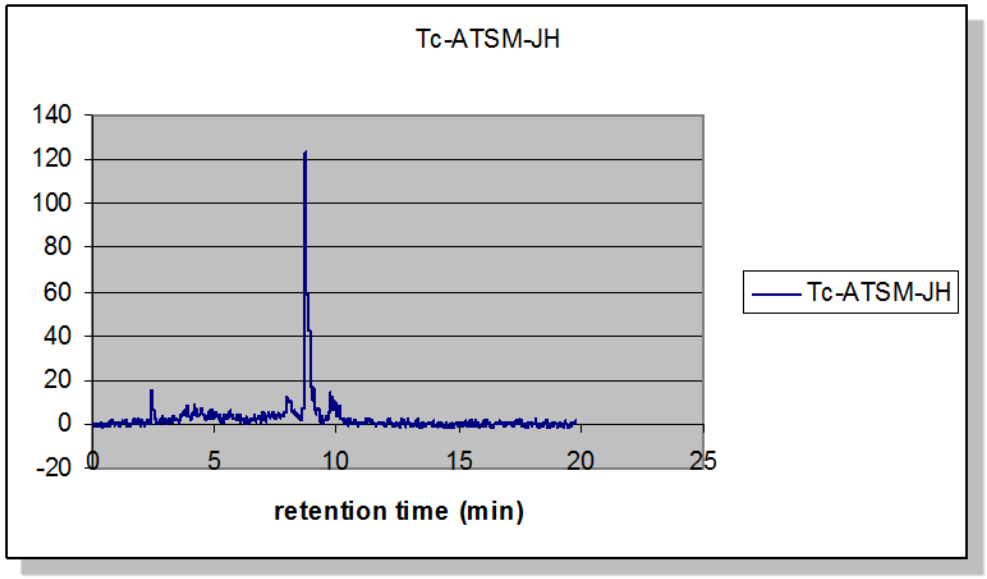
99m-Tc labelling of bis(thiosemicarbazones)



Compound prepared by extensively modified version of literature method

Yokyama et al , J. Nucl. Med., 1976, 17, 2045

Dilworth, J. et all. J. Nucl. Med , 2008



Second generation ^{99m}Tc radiopharmaceuticals

- The ability to determine the exact molecular structure of the coordination compounds using powerful modern analytical tools helped researchers to understand the structure–activity relationships underlying the biological behaviour of the ^{99m}Tc agents.
- As a consequence, careful design of new ligands and their ^{99m}Tc complexes led to the discovery of imaging agents for perfusion in the myocardium and brain.
- The widely used cardiac imaging agents ^{99m}Tc-MIBI (sestamibi, Cardiolite®) and ^{99m}Tc-tetrofosmin (Myoview®), and the brain imaging agents ^{99m}Tc-HMPAO (exametazime, Ceretec®) and ^{99m}Tc-ECD (bicisate, Neurolite®) are the result of the above strategy in the development of ^{99m}Tc complexes.
- The in vivo behaviour of these radiopharmaceuticals is driven by their molecular properties, such as size, charge and lipophilicity.
- These products, including the novel renal agent ^{99m}Tc-MAG3 (Mertiatide) and hepatobiliary agents such as ^{99m}Tc-mebrofenin, are generally referred to **as second generation ^{99m}Tc radiopharmaceuticals**.

Third generation ^{99m}Tc radiopharmaceuticals

- Current designs of imaging agents are based on the careful selection of ***suitable biomolecules to function as effective vectors for in vivo delivery of Tc-99m to more specific biological targets such as receptors and transporters.***
- **This strategy implies that the labelling approach employed for introducing a radionuclide into a biomolecule *should not lead to any distortion of that part of the molecule responsible for its biological activity*. Thus, these agents have required the development of sophisticated labelling approaches that go beyond the technologies previously used.**
- **The introduction of the bifunctional chelating agent (BFCA) concept and new chemistries such as the Tc-tricarbonyl, Tc-nitrido, Tc-HYNIC and mixed ligand complexes have helped to achieve that objective.**

- The radiopharmaceuticals ^{99m}Tc-HYNICEDDA-TOC are the best examples of third generation ^{99m}Tc radiopharmaceuticals. It is the first, and to date the only, ^{99m}Tc compound **for receptor studies in the brain**.

Part II

Compounding of radiopharmaceuticals in hospital radiopharmacies

- The compounding of ^{99m}Tc radiopharmaceuticals involves the addition of $^{99m}TcO_4^-$ eluted from a generator using to special kits at room temperature or with heating.
- ***Estimation of the radiochemical purity of the final product is made by*** use of chromatographic techniques such as paper chromatography (PC), instant thin layer chromatography (ITLC) or high performance liquid chromatography (HPLC) prior to administration to patients :
- http://www.youtube.com/watch?v=FbNqk5fV1gY
- Guidelines for aseptic compounding and dispensing of radiopharmaceuticals are available in the national Pharmacopeia.
- Radiopharmaceuticals are considered to be sterile products, compounding of ^{99m}Tc radiopharmaceuticals being carried out in an ISO 5 (class 100, grade A) laminar flow bench located in a clean room (with a buffer zone) = GMP .
- *Technetium-99m radiopharmaceuticals : manufacture of kits. — Vienna : IAEA, 2008. p. ; 24 cm. — (Technical reports series, ISSN 0074–1914 ; no. 466)*

GMP & Tc-RP production

FIG. 3.4(a)–(c). Internal views of a kit production facility; see text for explanation of figures (source: Monrol A.S.).

IAEA, 2008. p. ; 24 cm. — (Technical reports series, ISSN 0074–1914 ; no. 466)

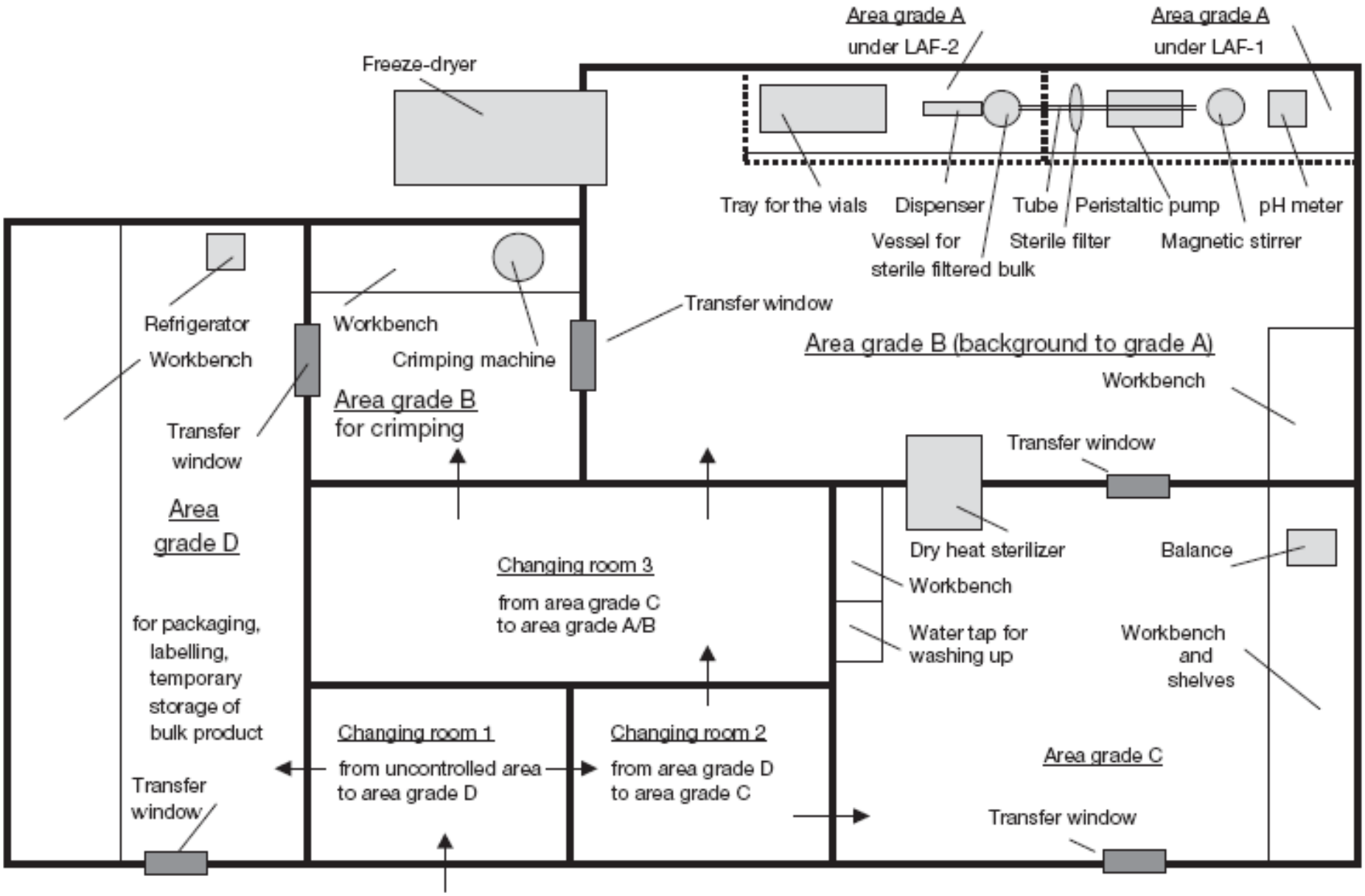


FIG. 3.3. Typical layout of a kit production laboratory.

IAEA, 2008. p. ; 24 cm. — (Technical reports series, ISSN 0074–1914 ; no. 466)

Sn(II) content assay

- Most kits for Tc-99m radiopharmaceuticals employ Sn(II) ions to reduce it from +7 to the desired oxidation state.
- **The amount of Sn(II) is variable. It is important to maintain at least minimum Sn(II) level, when parallel reduction reactions could occur as very low amounts of Sn(II) will result *in incomplete reduction* of technetium. High amounts could damage the compound formed**.

- One such example is the kit for ^{99m}Tc-HMPAO:
- It is often necessary to measure the Sn(II) content in the kit vial. Estimation of the Sn(II) content could be carried out by simple methods such as titration with iodine or N-bromosuccinimide. However, interference owing to the presence of other reducing agents is possible, and it is necessary to ensure that such interference does not occur. **Radiochemical purity test is imperative**.

TECHNETIUM-99m RADIOPHARMACEUTICALS: MANUFACTURE OF KITS

- IAEA - TECHNICAL REPORTS SERIES No. 466 - VIENNA, 2008
- http://www.iaea.org/books

EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES, Technetium (99mTc) medronate injection, European Pharmacopoeia, 5th edn, EDQM, Council of Europe, Strasbourg (2005) 859.

Manufacturer Instructions

PREPARATION OF KIT FOR ^{99m}Tc-MDP

- **Reagents**

- **Methylene diphosphonic acid** (MDP);
- Ascorbic acid;
- Stannous chloride dihydrate: $SnCl_2 \cdot 2H_2O$;
- Hydrochloric acid: HCl (concentrated, 1N, 0.2N);
- Sodium hydroxide: NaOH (1N);
- Water for injection; Nitrogen gas.

Tc-MDP kit

Chemical composition of kit

- Methylene diphosphonic acid (MDP) : 10 mg;
- $SnCl_2x2H_2O$: 1 mg;
- Ascorbic acid: 2 mg.

7.1.3. Manufacturing formulas

Final volume (mL)	MDP (g)	Ascorbic acid (g)	Stannous chloride dihydrate (g)
100	1.0	0.2	0.1
250	2.5	0.5	0.25
500	5.0	1.0	0.5
800	8.0	1.6	0.8
1000	10.0	2.0	1.0

Preparation of kit solution for a final volume of 500 mL

Use water for injection bubbled with nitrogen gas. Solution A: Dissolve 500 mg of stannous chloride dihydrate using 50 mL of 0.2N HCl (or 0.4 mL of concentrated HCl, adjusting the volume to 50 mL) just before it is added to the final solution. Dissolve 5 g of MDP in approximately 400 mL of water for injection. Add 1 g of ascorbic acid; the pH will be in the range of 3.5–4.0 after the addition. Slowly add solution A to the MDP solution, with continuous N2 bubbling and stirring. Adjust the pH to between 4 and 5 using 1N NaOH or 1N HCl. Adjust the final pH to 5.8–6.0 using a pH meter. Adjust the final volume to 500 mL. Filter the solution through a sterile 0.22 µm filter. Dispense 1 mL per vial.

Freeze-dry using the following conditions:

Freeze temperature	Dried temperature	Time
-30ºC	24ºC	24–48 h

Store refrigerated at 2–8ºC.

Tc-MDP kit (Methylene diphosphonic acid)

- **Radiolabelling**
- Reconstitute the freeze-dried kit using 4 mL of freshly eluted 99mTcO4 solution containing a maximum of 500 mCi (18.5 GBq) of activity.
- Stir for 1 min and use after 5 min.
- The 99mTc-MDP labelled in this manner should be stable for over 6 h after labelling.
- **Labelling features**
- MDP: 2.5 mg/mL;
- Stannous chloride dihydrate: 0.25 mg/mL;
- pH: 5–7; Radiochemical purity: >95%;
- Pertechnetate (TcO4 –) + 99mTc reduced/hydrolysed: <5%.
- **Quality control analyses**
- Radiochemical purity: Ascendinghromatography

Support	ITLC-SG or Whatman No. 1 paper	ITLC-SG
Solvent	MEK/acetone	Saline
R_f ^{99m}Tc-MDP	0.0	0.9–1.0
R_f $^{99m}TcO_4^-$	0.9–1.0	0.9–1.0
R_f ^{99m}Tc reduced/hydrolysed	0.0	0.0

Note: MEK: methyl ethyl ketone.

Main ingredients content:
Determination of the content of MDP may be required by local regulations. The average amount of $SnCl_2$ must be at least 50% of the expected value. A non-radioactive formulation should dissolve easily in saline, giving a clear and colourless solution.

Biodistribution: The typical biodistribution pattern of 99mTc-MDP in mice at 2 h post-injection is as follows:

Organ	%i.d./organ	%i.d./g
Bone (femur)	≥60	≥2
Liver	≤3	≤1
Kidneys	≤5	≤1

Instructions from Pharmacopeia and the kit Supplier may differ to some extent due to special features of the latter : www.nuclearonline.org/PI/BRACCO%20MDP%20doc.pdf :

BRACCO
DIAGNOSTICS

MDP-BRACCO™
Kit for the Preparation of Technetium Tc 99m Medronate
For Diagnostic Use

DESCRIPTION
Each reaction vial contains a sterile, nonpyrogenic, nonradioactive lyophilized mixture of 20 mg medronic acid, 11 mg sodium hydroxide, 1 mg ascorbic acid, 0.13 mg (minimum) stannous fluoride, SnF_2; and 0.38 mg total tin, maximum (as stannous fluoride, SnF_2). The pH is adjusted with sodium hydroxide or hydrochloric acid to 6.5 (6.3 to 6.7) prior to lyophilization. The vial does not contain a preservative. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 5.4 to 6.8. The structure of medronic acid is given below:

Tec-Control Chromatography Systems *BIODEX, …*

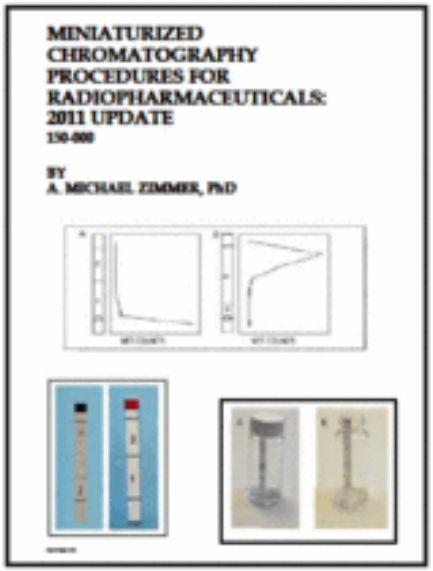
- **For radiopharmaceutical quality control**

Tec-Control Chromatography tests the radiochemical purity of specific Tc-99m-labeled radiopharmaceuticals.

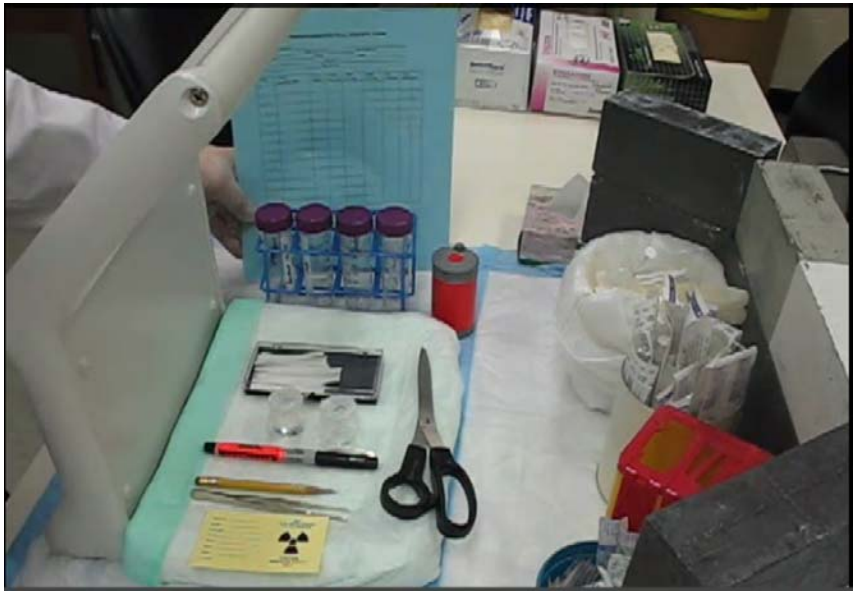
- The accompanying chart shows which strips and solvents are required to perform each individual test.
- Some solvents must be purchased separately (see Sigma-Aldrich chart) due to hazardous material shipping restrictions.
- Detailed instruction manuals are packaged with each strip container, although our Radiopharmaceutical QC Procedure Manual (151-000) explains paper chromatography in greater detail.

Radiochemical purity tests

- Tests with ITLS
- Could be followed at YOUTYBE:
- http://www.youtube.com/watch?v=FbNqk5fV1gY



Manual written by Michael Zimmer



Detailed manual explains Paper Chromatography, a QC method for evaluating the radiochemical purity of currently used Tc-99m-labeled RadPh. Procedures are quick and easy to use, a simple quality control solution for any nuclear medicine department.

PREPARATION OF KIT FOR ^{99m}Tc- MAG_3

- **Reagents**
- S-benzoylmercaptoacetyl-tryglicine (MAG_3);
- $SnCl_2.2H_2O$;
- Disodium glucoheptonate;
- Disodium tartrate dihydrate;
- Lactose;
- Hydrochloric acid: HCl (concentrated, 1N, 0.2N, 0.001N);
- Sodium hydroxide: NaOH (1N);
- Water for injection;
- Nitrogen gas.

Chemical composition of kit

- MAG_3: 1 mg;
- Disodium glucoheptonate: 20 mg;
- Disodium tartrate dihydrate: 40 mg;
- Lactose: 20 mg;
- Stannous chloride dihydrate: 0.1 mg.

PREPARATION OF KIT FOR ^{99m}Tc- MAG_3

Preparation of kit solution for a final volume of 100 mL

- *Use cold water for injection bubbled with nitrogen gas*.
- Solution A: Dissolve 100 mg of stannous chloride dihydrate using 10 mL of 0.2N HCl (or 0.5 mL of concentrated HCl, adjusting the volume to 10 mL) just before it is added to the final solution.
- Dissolve 100 mg of MAG3 in approximately 80 mL of water for injection.
- Add 2.0 g of disodium glucoheptonate and 4.0 g of disodium tartrate dihydrate and allow to dissolve.
- Slowly add 1 mL of solution A, with continuous N2 bubbling and stirring.
- Control the pH at between 4 and 5, using 1N NaOH or 1N HCl. Adjust the final pH to 5.0–5.5 using a pH meter. Add 2.0 g of lactose and allow to dissolve. Adjust the final volume to 100 mL. Filter the solution through a 0.22 µm sterile filter. Precool the vial inside the freeze-dryer or using liquid nitrogen.
- Dispense 1 mL per vial, keeping the vials as cool as possible.

PREPARATION OF KIT FOR ^{99m}Tc- MAG_3

Radiolabelling

- Reconstitute the freeze-dried kit using 3 mL of freshly eluted $^{99m}TcO_4$ solution containing a maximum of 100 mCi (3.7 GBq) of activity. Stir for 1 min. Allow to stand for 5 min.
- Heat the vial in a boiling water bath for 15 min and allow to cool to room temperature.
- The ^{99m}Tc-MAG_3 labelled in this manner should be stable for over 6 h after labelling.

Quality control analyses

- Activate a Sep-Pak C-18 column with 5–10 mL of ethanol.
- Wash with 5–10 mL of 0.001N HCl.
- Add 0.1 mL of 99 mTc-MAG3 and elute the column as follows, counting each fraction:
- A : Eluent contains 99mTcO4, 99m Tc-reduced/hydrolysed, etc.
- B: Elute with 10 mL of ethanol:saline (1:1, vol./vol.); eluent contains 99mTc-MAG3
- C: Activity in column

Radiochemical purity 100B/(A+B+C), %

- Elute with 10 mL of 0.001N HCl.

^{99m}Tc-MAG$_3$ Radiochemical purity: Ascending chromatography

Support	ITLC-SG	ITLC-SG or Whatman No. 1 paper
Solvent	Octanol	Saline
R_f ^{99m}Tc-MAG$_3$	0.0	0.9–1.0
R_f $^{99m}TcO_4^-$	0.9–1.0	0.9–1.0
R_f ^{99m}Tc reduced/hydrolysed	0.0	0.0

The typical biodistribution of ^{99m}Tc-MAG$_3$ in rats at 30 min post-injection:

Organ	%i.d./organ
Kidneys	≤2
Bladder and urine	≥80
Liver	<2

EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES, Technetium (99mTc) mertiatide injection, European Pharmacopoeia, 5th edn, EDQM, Council of Europe, Strasbourg (2005) 860.

Another example : Sulphur-Tc colloid

PREPARATION OF KIT FOR ^{99m}Tc- SULPHUR COLLOID

- **Reagents:**
- Sodium thiosulphate pentahydrate;
- $NaH_2PO_4.2H_2O$; $Na_2HPO_4.2H_2O$;
- HCl (conc., 0.3N); HNO_3; NaOH (1N); 3.5% gelatin solution; Water for injection; N_2 gas.

Component A:

Final volume (mL)	Concentrated HCl (mL)
100	1.5
250	3.75

Component B:

Final volume (mL)	3.5% gelatin solution (mL)	10% sodium thiosulphate solution (mL)
100	85	10
250	212.5	25

Component C:

Final volume (mL)	Disodium dihydrogen phosphate dihydrate (g)	Sodium dihydrogen phosphate dihydrate (g)
100	13.6	1.2
250	34.0	3.0

- **Chemical composition of kit**
- The kit comprises three different components necessary for preparation
- of the radiopharmaceutical:
- Component A: 0.5 mL of 0.3N HCl;
- Component B: 1 mL of solution containing 10% **sodium thiosulphate** and 3.5% **gelatin**;
- Component C: 1 mL of 0.08M **phosphate buffer** at pH7.4 containing 136 mg of Na2HPO4 and 12 mg of NaH2PO4.

PREPARATION OF KIT FOR ^{99m}Tc- SULPHUR COLLOID

- **Preparation of kit solution / final V = 100 mL** - Use cold water for injection bubbled with N2 gas, and bubble N2 gas while preparing the solutions !
- **Component A:** To 1.5 mL of concentrated HCl, add 53.5 mL of water for injection with stirring. Mix thoroughly and filter through a 0.22 µm membrane filter. Dispense 0.5 mL aliquots per vial into sterile 10 mL vials.
- **Component B:** Prepare 100 mL of 3.5% gelatin solution and sterilize in an autoclave.
- Weigh 1.5 g of sodium thiosulphate pentahydrate and dissolve in 10 mL of water for injection. Mix well and adjust the volume to 15 mL with water for injection to obtain 10% thiosulphate solution.
- Add 10 mL of the 10% sodium thiosulphate solution to 85 mL of 3.5% gelatin solution. Mix well and dispense 1 mL aliquots into 10 mL clean sterile vials under aseptic conditions. Autoclave the vials.
- **Component C:** Weigh 1.2 g of sodium dihydrogen phosphate dihydrate and 13.6 g of
- disodium dihydrogen phosphate dihydrate. Dissolve in 80 mL of water for injection.
- Mix well and adjust the volume to 100 mL with water for injection. Filter the solution through a sterile 0.22 µm filter. Dispense 1 mL aliquots into sterile 10 mL vials
- *Store components A and C at 20-25^{o}C, and component B refrigerated at 2–8ºC.*

PREPARATION OF KIT FOR ^{99m}Tc- SULPHUR COLLOID

Radiolabelling

- Add 3 mL of $^{99m}TcO_4$ solution containing a maximum of 100 mCi (3.7 MBq) of activity to component A.
- Transfer 0.5 mL of component B to the reaction vial containing component A.
- Mix well and place the vial in a boiling water bath for 3–5 min.
- Allow the vial to cool to room temperature (5 min) and then transfer
- 0.5 mL of component C into the reaction vial and mix; use after 5 min.
- Biodistribution:

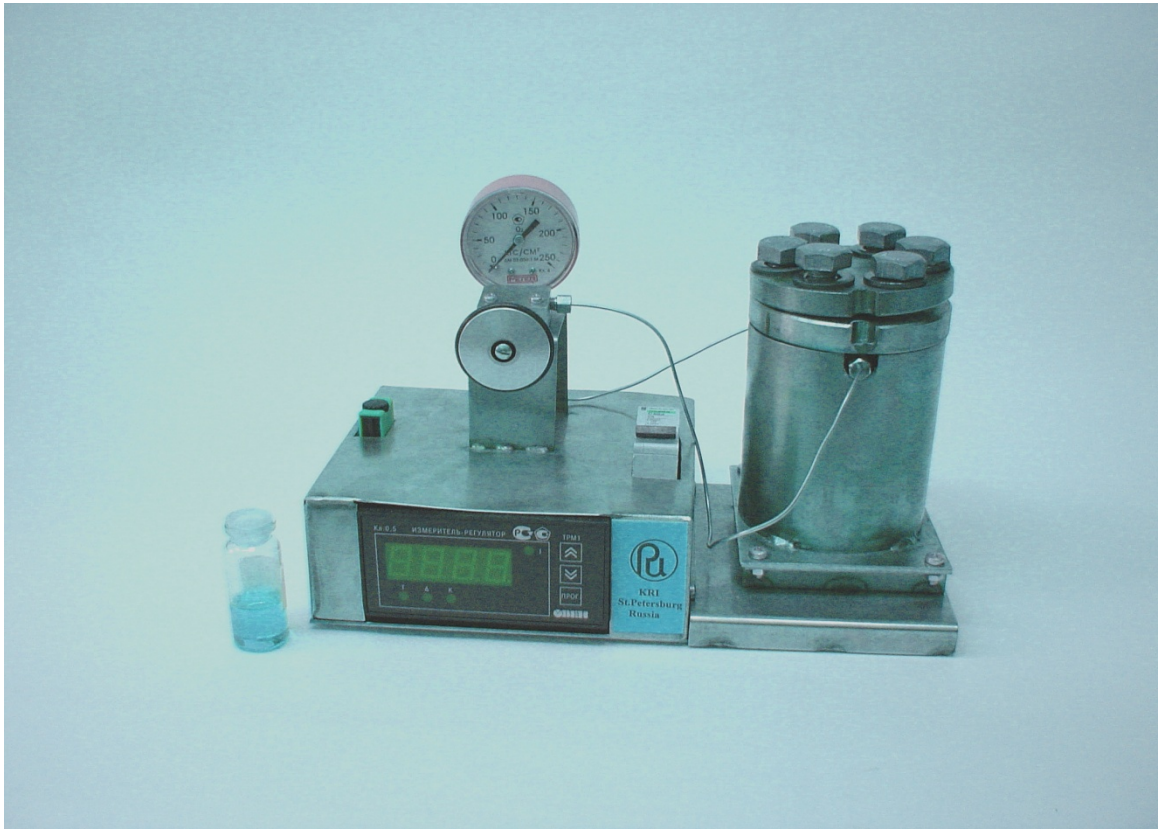
Organ	%i.d./organ
Liver and spleen	>80
Lungs	≤5

- **Labelling features**
- 99mTc-sulphur colloid: colloidal suspension; pH: 4–7; Radiochemical purity: >95%;
- Free pertechnetate (TcO_4–): <5%.and mix; use after 5 min.
- **Quality control analyses**
- Radiochemical purity: Ascending chromatography

Support	ITLC-SG or Whatman No. 1 paper
Solvent	Acetone or saline
R_f ^{99m}Tc-sulphur colloid	0.0–0.1
R_f $^{99m}TcO_4^-$	0.9–1.0

EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES, Technetium (99mTc) colloidal sulphur injection, European Pharmacopoeia, 5th edn, EDQM, Council of Europe, Strasbourg (2005) 852.

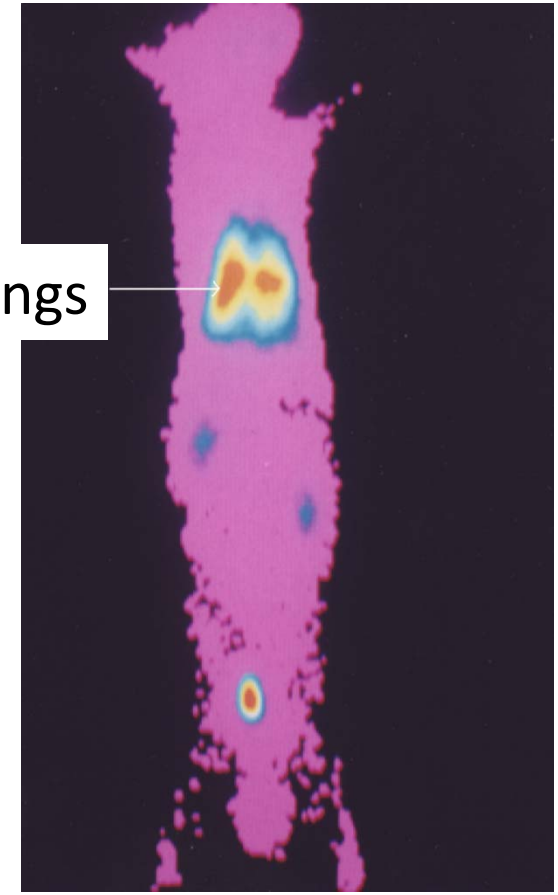
Mini-Autoclave for Generation of $^{99m}TcI(CO)_5$ (with CO source)



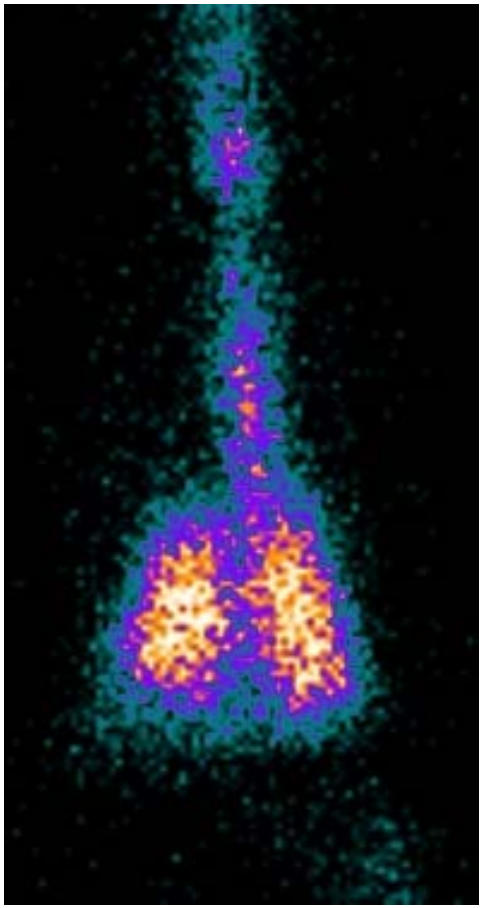
$K^{99m}TcO_4$ (eluate) + CO + HI → $^{99m}TcI(CO)_5$
(transferred through the gas phase during relief of CO)

(Miroslavov, Sidorenko , A.N. Yalfimov - ISTR-2011)

Accumulation of $^{99m}TcI(CO)_5$ in Lungs of Rabbits



Intravenous injection



Inhalation

(Miroslavov, Sidorenko , A.N. Yalfimov - ISTR-2011)

Tc in Nuclear medicine problems and discussions

Mo-99 - Tc-99 Generator

- Problem of Mo99 – Tc99 generator inaccessibility, NRU reactor shutdown period
- ***For 4 decades Mo-99 has been produced based on HEU – Global Threat Reduction Initiative (GTRI)***
- Use of LEU for Mo-99 generators production
- Alternative methods for Mo-99

Tc symposiums

- Italian TERACHEM (Prof. U. Mazzi) 1985 – 2010
- IST / ISTR (Joshihara, Sekine …) 1993 – 2014 (Japan, Russia, S. Africa, France?…)
- Radiopharmaceutical Soc. Symp.

Alternative production routes for ^{99}Mo

Full-scale production of Mo-99 using accelerators.

- **Photonuclear reaction :**
- **Mo-100 (γ,n) Mo-99**
- **240 – 400 μCi produced in two tests with natural Mo target**
- **Tested with North Star Medical Radioisotopes ARSII generator**

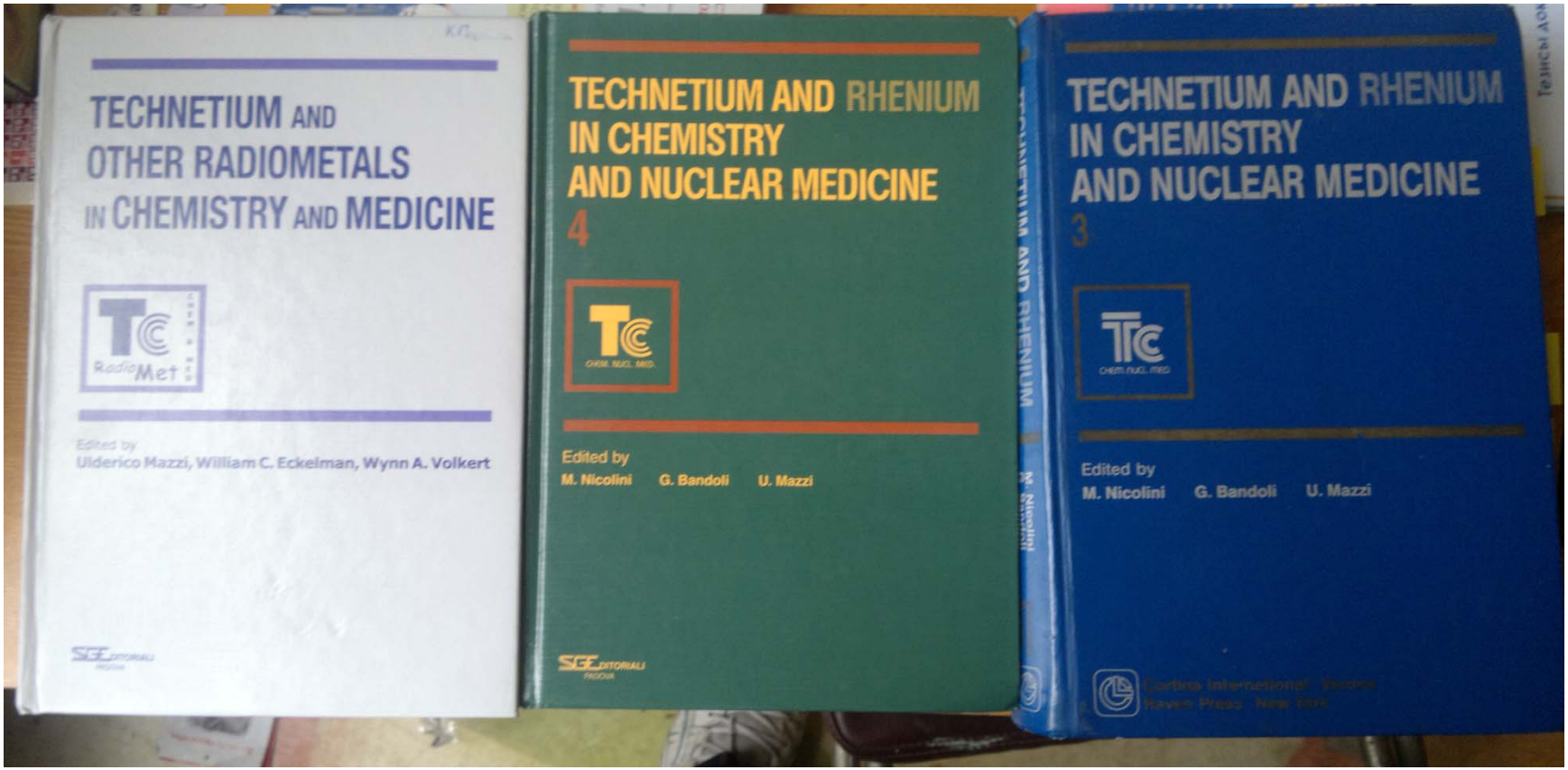
- **Mo-100(p,2n)Tc-99m accelerator driven transform at 22 MeV protons**

Neutron capture technology

- Nuclear reaction:
- **Mo-98(n,γ)Mo-99**
- 10 days of irradiation at nuclear reactor

- Fail of international efforts in providing large scale production of **Mo-99 from LEU** at NIIAR reactor in Russia
- The price of Tc-99m injection raised by factor of 5 in 2 years !
- Concentration at supply of Mo-99 to USA, Japan, Western Europe

What to read : Ulderico Mazzi and others
7 great books of Proceedings series (1987 – 2010)



What to read (books available on-line): Series IST , ISTR (Japan – Russia - … International Symposiums) (1993 – 2011 and … 2014)

http://www.technetium-99.ru/history1.html

http://www.technetium-99.ru/IntSympTcRe-2011.pdf