

Pulmonary Perfusion Imaging Using Tc-99m MAA

1. OVERVIEW

- a) Tc 99m Macroaggregated Albumin (MAA) is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients.
- b) Tc-99m MAA may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (LeVeen) shunt patency.
- c) The radiopharmaceutical Tc-99m MAA is used in the perfusion phase of a ventilation/perfusion (V/Q) scan to assess the flow of blood in the lungs.
- d) Combining a pulmonary perfusion and ventilation study increases both the diagnostic sensitivity and specificity of the V/Q scan.
- e) A V/Q scan provides diagnostic clarity comparable to CTPA with less risk of radiation overexposure.

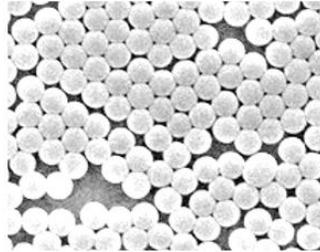
2. RADIOPHARMACEUTICAL UTILIZED

- a) The only radiopharmaceutical currently available for imaging perfusion in the lungs, Tc-99m Macroaggregated Albumin (Tc-MAA), is actually a radiolabeled, precipitated, biodegradable macroaggregate of human serum albumin. It is prepared under carefully controlled conditions of pH, time, temperature, agitation, and reagent concentration to insure correct particle size formation. The biological half-life in capillaries is approximately 2-3 hours.
- b) Just a historical note- Many years ago, there was a commercially available Tc-99m lung perfusion agent called HAM (**H**uman **A**lbumin **M**icrospheres). It was also a radiolabeled, precipitated, biodegradable macroaggregate of human serum albumin; however, it was precipitated in oil rather than in aqueous solution. This resulted in the formation of perfectly spherical particles rather than amorphous-

shaped ones. The particle size range of HAM was very similar to that of MAA. Chemical composition was essentially identical to that of Tc-MAA.

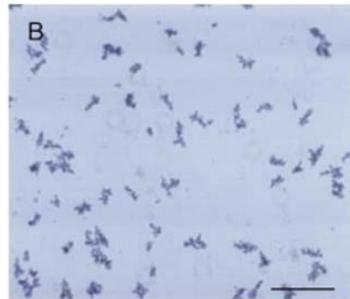
c) Microscopic appearance of microspheres and macroaggregates

Photomicrograph of Microspheres



Note the size uniformity of the particles

Photomicrograph of Tc-99m MAA Particles



The solid bar represents 100 μm . Note lack of uniformity of size and shape.

- d) As specified by the FDA, at least 90% of all particles must be in the range of 10-90 μm . This range was chosen to ensure that particles smaller than the 7-8 μm diameter of capillaries would be absent, eliminating the possibility of localization in the brain, kidneys, and other internal organs. On the high end, 90 μm was chosen to minimize the risk of occlusion of larger vessels, especially in the patient with pulmonary artery hypertension, in which case vasoconstriction is present.
- e) The official particle size limits, set more than 40 years ago by the FDA, are

90% of all particles must be 10-90 μm

and

No particle may be > 150 μm in its longest aspect

- f) Since each injection embolizes hundreds of thousands of capillaries, one must be concerned about patient safety. In fact, the margin of safety for patients injected with Tc-99m MAA is enormous: the adverse reaction rate in the US for Tc-99m MAA is approximately 2/100,000 injections, an outstanding track record. This safety record is attributable to the very small fraction of the pulmonary vasculature that is occluded by the typical injection of Tc-MAA. That number is typically quoted to be < 0.1%, or < 1 capillary in 1,000. This implies that 99.9% of all capillaries are patent.
- g) It is critical to control the number of particles injected into each of 4 categories of patients:

Ideal number of particles to be injected

50K particles in neonate

100-350K in children 1-18 (scale by mass)

150K particles in patients with known pulmonary hypertension

200-700K particles in “normal” patients

Use of Tc-99m MAA is contraindicated in patients with severe pulmonary hypertension

3. CHARACTERISTICS OF THE RADIONUCLIDE

- a) Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies has a percent abundance of 89.07 % and the energy is 140.5 KeV.
- b) The specific gamma ray constant for Tc 99m is 0.78 R/millicurie-hr at 1 cm.
- c) The first half-value layer is 0.017 cm of lead (Pb) and the first tenth value layer is 0.08 cm of Pb.

4. DRUG AVAILABILITY

- a) Jubilant DraxImage is the sole supplier of Sn-MAA kits in North America. The company is committed to maintaining its availability for healthcare professionals.

5. MOLECULAR STRUCTURE

- a) To date, no one has ever elucidated the actual molecular structure of Tc-MAA. This is not surprising since the molecular weight of MAA is ~66,500. As stated in the package insert, "The precise structure of the stannous-technetium-albumin complex is unknown at this time."
- b) We do know that there are numerous binding sites on albumin for metals, which account for binding of Tc-99m and other radiometals to MAA.

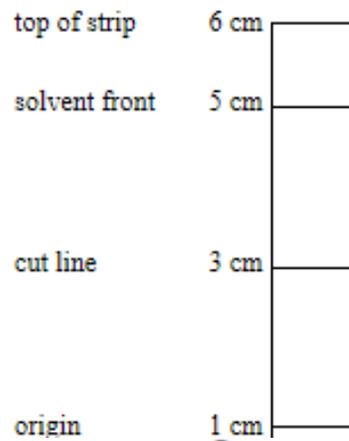
6. DRUG PREPARATION PROCEDURE

- a) Na pertechnetate solution (min volume: 5.0 ml, max volume 10 ml) is aseptically added to reaction vial.
- b) In choosing the activity of Tc-99m to be used in the preparation, the labeling efficiency, number of patients, administered radioactive dose, number of particles per vial, and radioactive decay must be taken into account. The maximum amount of Tc-99m to be added to the Reaction Vial is 2.22 GBq (60 mCi).
- c) Agitate shielded reaction vial for a few sec; let stand for at least 15 min at room temperature.
- d) Prior to withdrawing a dose, gently agitate vial to effect homogeneous suspension of the Tc-MAA. To maintain nitrogen atmosphere and prevent oxidation, do not vent the vial.
- e) Store the shielded reaction vial at 2°C to 8°C when not in use and discard after 6-8 hours from the time of preparation.

7. QUALITY CONTROL PROCEDURES

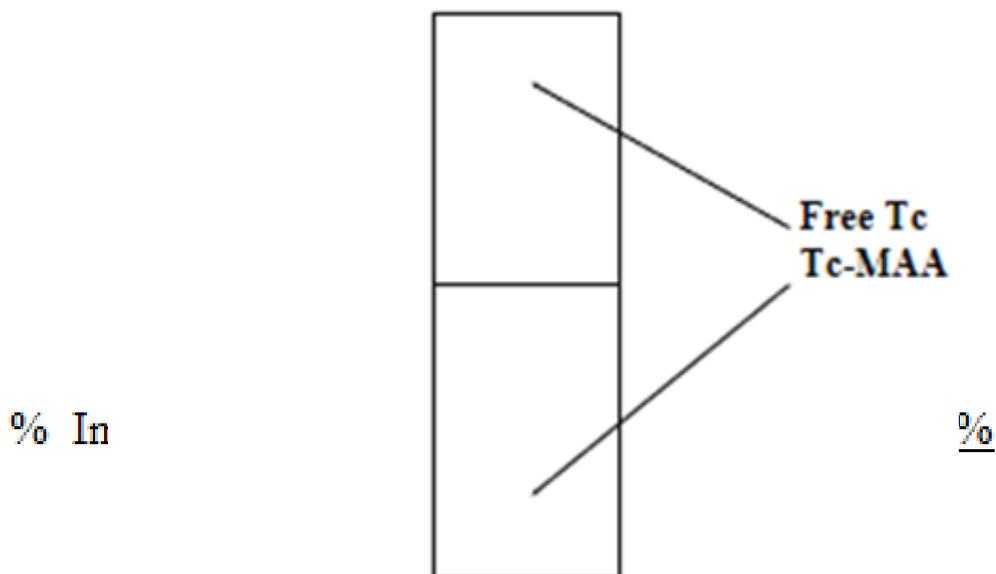
Performed by thin layer or paper chromatography in which the radiopharmaceutical is spotted on the "origin" of the strip (see diagram at right) and the strip is placed into a glass vial containing the appropriate solvent. The solvent climbs to the "solvent front" line and then the strip is removed and cut in half. Each half is counted in an appropriate radioactivity measurement device and the % Radiochemical Purity is then calculated.

STRIP DESIGN



Migration Pattern of Tc-MAA

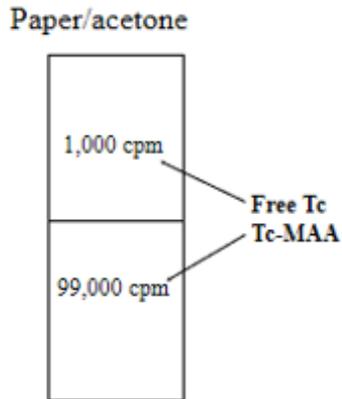
Paper/acetone



$$\text{Labeling efficiency} = 100\% - \% \text{ Free Tc}$$

For insoluble Tc-99m Radiopharmaceuticals (e.g., Tc-MAA, Tc-SC), it is only necessary to test for the presence of free Tc. No simple system can effectively separate colloidal HR Tc from an insoluble product, so HR Tc cannot be measured in these products. We therefore ignore its presence.

What is Radiochemical Purity of Tc-MAA?



Results

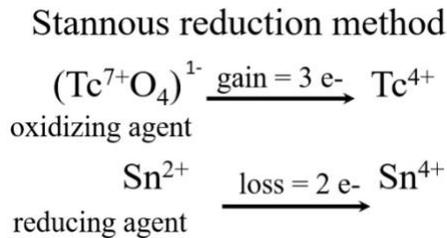
$$\% \text{ free Tc} = 1,000 / (1,000 + 99,000) = 1\%$$

therefore,

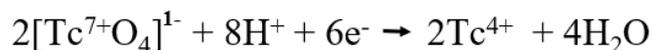
$$\% \text{ Tc-MAA} = 100\% - 1\% = 99\%$$

8. RADIOCHEMICAL REACTION

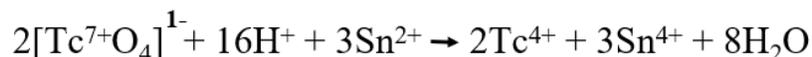
- a) It is necessary to convert the electronegative pertechnetate to an electropositive form as it is unable to react with the electronegative anions on the protein molecule due to repulsion. That conversion of pertechnetate takes place via a reduction/oxidation reaction as shown below.



- b) Tc^{4+} then reacts with the electronegative ions on the protein molecule to form a Tc-MAA complex.
- c) Overall Redox Reaction



THEREFORE,



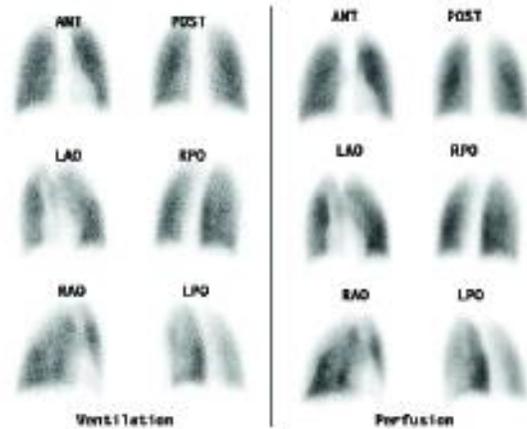
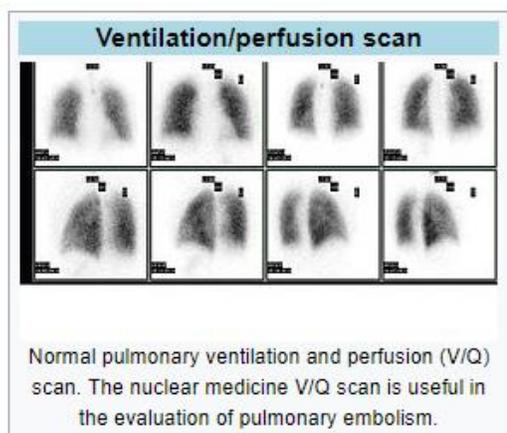
9. CLINICAL PHARMACOLOGY

- a) Immediately following intravenous injection, more than 80% of the albumin aggregated is trapped in the pulmonary alveolar capillary bed. The imaging procedure can thus be started as soon as the injection is complete. Assuming that a sufficient number of radioactive particles has been used, the distribution of radioactive aggregated particles in the normally perfused lung is uniform throughout the vascular bed, and will produce a uniform image. Areas of reduced perfusion will be revealed by a corresponding decreased accumulation of the radioactive particles, and are imaged as areas of reduced photon density.
- b) Organ selectivity is a direct result of particle size. Below 10 micrometers, the material is taken up by the reticuloendothelial system. Above 10 micrometers, the aggregates become lodged in the lung by a purely mechanical process. Distribution of particles in the lungs is a function of regional pulmonary blood flow.
- c) The aggregated albumin is sufficiently fragile for the capillary micro-occlusion to be temporary. Erosion and fragmentation reduce the particle size, allowing passage of the aggregates through the pulmonary alveolar capillary bed. The fragments are then accumulated by the reticuloendothelial system.
- d) Lung to liver ratios greater than 20:1 are obtained in the first few minutes post-injection. Elimination of the Tc 99m aggregated albumin from the lungs occurs with a half-life of about 2 to 3 hours.
- e) Cumulative urinary excretion studies show an average of 20% elimination of the injected technetium Tc 99m dose 24 hours post-administration. Following administration of technetium Tc 99m albumin aggregated by intraperitoneal injection, the radiopharmaceutical mixes with the peritoneal fluid. Clearance from the peritoneal cavity varies from insignificant, which may occur with complete shunt blockage, to very rapid clearance with subsequent transfer into the systemic circulation when the shunt is patent.
- f) Serial images should be obtained of both the shunt and lung (target organ). However, an adequate evaluation of the difference between total blockage of the shunt and partial blockage may not be feasible in all cases.

10. MECHANISM OF LOCALIZATION OF RADIOPHARMACEUTICAL:

- a) Following an intravenous injection of Tc-MAA, occlusion of the capillaries takes place due to the fact that the particle size of Tc-MAA (10-90 μm) is much larger than the diameter of the average capillary (7-8 μm). The mechanism of localization of Tc-MAA in pulmonary capillaries is known as **Capillary Blockade**, which typically results in the microembolization of hundreds of thousands of capillaries in the lungs of adults. Fewer particles are administered to pediatric patients, but the fraction of capillaries occluded is probably similar to that of adults.

11. NORMAL LUNG SCANS



12. INDICATIONS FOR LUNG PERFUSION SCANNING

- Determine the likelihood of pulmonary embolism.
- Document the degree of resolution of pulmonary embolism.
- Quantify differential pulmonary function before surgery for lung cancer
- Evaluate lung transplants
- Evaluate congenital heart or lung disease such as cardiac shunts, pulmonary arterial stenoses, and arteriovenous fistulae and their treatment
- Confirm the presence of bronchopleural fistula
- Evaluate chronic pulmonary parenchymal disorders such as cystic fibrosis
- Evaluate the cause of pulmonary hypertension
- hepatopulmonary syndrome
- FEV1 calculation in lung surgery planning
- selective internal radiation therapy planning
- venography for deep venous thrombosis

13. TYPICAL ADMINISTERED DOSE FOR ADULTS

- a) The usual administered activity for adult patients is 74–148 MBq (2-4 mCi) injected intravenously.
- b) For markedly obese adult patients, the administered activity may be increased to 5-6 mCi.
- c) For pediatric patients, the recommended activity to be injected is 9–11 MBq/kg (250–300 μ Ci/kg), with a minimum of 20–40 MBq (0.54–1.08 mCi).
- d) The maximum administered activity for pediatric patients should not exceed the administered activity for an adult.

14. PATIENT PREPARATION FOR LUNG IMAGING

- a) The rationale for performing the procedure and the details of the procedure itself should be explained to the patient in advance.
- b) A standard chest radiograph in both posterior–anterior and lateral projections is preferred. A portable anterior–posterior chest radiograph is acceptable only if the patient cannot tolerate a routine chest radiographic examination. In patients who have no changes in signs or symptoms, a chest radiograph within a few days may be adequate.
- c) A CT scan can substitute for the chest radiography.

(adapted from SNM Practice Guideline for Lung Scintigraphy 4.0)

15. DRUG ADMINISTRATION PROCEDURE

- a) The injection is performed intravenously over a period of a few seconds.
- b) A small volume of blood is drawn back into the syringe and then re-injected to insure complete delivery of the bone agent.
- c) Hemostasis is accomplished using a gauze pad and pressure.
- d) The gauze pad at the injection site is covered with a Band-Aid or tape.

16. ADVERSE REACTIONS FOLLOWING IV INJECTION OF Tc-MAA

Several adverse reactions have been reported. These were usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, chills, nausea and vomiting. They are very rare.

17. IMAGING PROTOCOLS

(adapted from “[SNMMI Practice Guideline for Lung Scintigraphy 4.0]” reprinted from http://interactive.snm.org/DOCS/LUNG_SCINTIGRAPHY_V4_FINAL.PDF, © SNMMI Inc.)

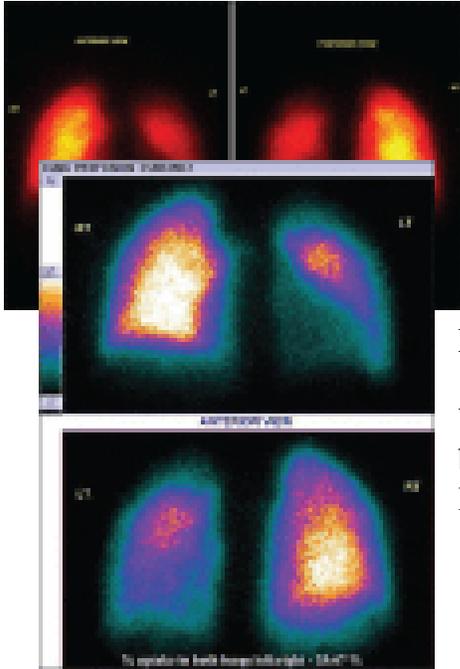
Image Acquisition: Perfusion imaging

- a) After the patient has been told to cough and take several deep breaths, ^{99m}Tc -MAA is injected slowly during 3–5 respiratory cycles with the patient supine. A well-flushed indwelling line can be used if venous access is difficult.
- b) The tracer should not be administered in the distal port of a Swan– Ganz catheter or any indwelling line or port that contains a filter—for example, a chemotherapy line.
- c) Imaging is preferably performed with the patient upright to increase chest cavity size and to minimize diaphragmatic motion. If necessary, images can be obtained with the patient in the supine or decubitus position. Planar images should be obtained in multiple projections including anterior, posterior, both posterior oblique, both anterior oblique, and both lateral projections.
- d) Either the anterior oblique or the lateral projections can be omitted. It may be possible to obtain only limited views in some patients.
- e) SPECT can be used to obtain a 3-dimensional evaluation of the perfusion and is recommended by some investigators. Imaging of high-blood-flow systemic organs can be used to detect right-to-left shunting.
- f) Images of the brain may be obtained to distinguish right-to-left shunting from systemic distribution of radiopharmaceutical components too small to be trapped by capillaries.

18. TYPICAL LUNG SCANS IN VARIOUS DISEASES

Case 1. Tc-99m MAA lung perfusion scan in pulmonary artery stenosis

Pre-left pulmonary artery stenting scan.

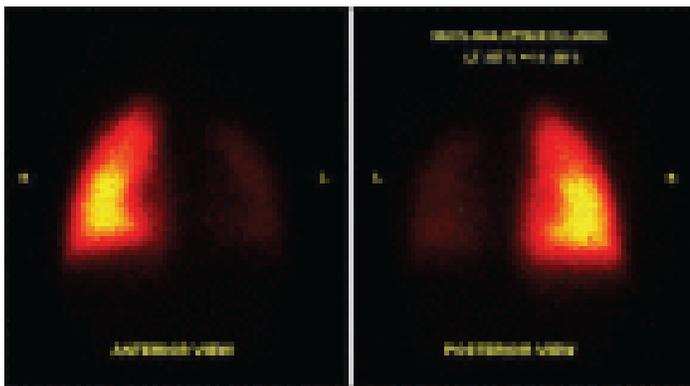


Significantly reduced Tc-99m MAA distribution in entire left bronchopulmonary segments. Percentage uptake in left:right lung segments is 29:71%

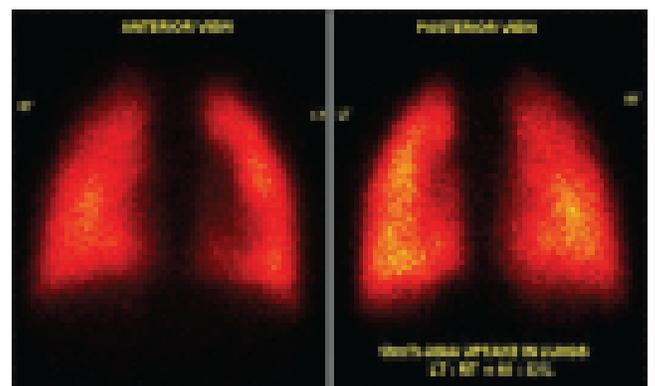
Post left pulmonary artery stenting scan.

Very minimal improvement in perfusion of left bronchopulmonary segments. Percentage uptake of left:right lung is 33:67%

Case 2. A 2-year-old child was a known case of congenital cyanotic heart disease. He underwent corrective surgery. On follow-up, he was found to have LPA stenosis. Lung perfusion scan showed differential perfusion of left: right lungs to be 11:89%. Patient underwent LPA stenting for severe LPA stenosis. Follow-up lung perfusion scan showed differential perfusion in left: right lung to be 48:52%. There was a significant improvement in differential perfusion of bilateral lungs post-treatment



Pre-surgical scan



Post-surgical scan

Case 3. Frontal slices in patient with massive PE. Absent perfusion in the right lung and sub-segmental defects in the left are clearly delineated.



Case 4. Frontal slices in a patient with COPD and PE. Ventilation is very uneven in the whole lung. In addition, multiple perfusion defects are seen in ventilated areas. Mismatch is highlighted in V/P quotient images

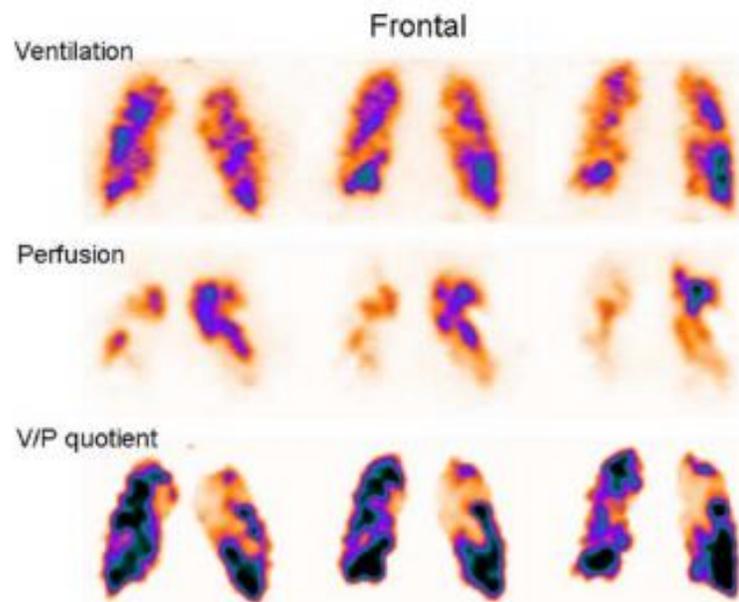


Fig. 5 Frontal slices in a patient with COPD and PE. Ventilation is very uneven in the whole lung. In addition, multiple perfusion defects are seen in ventilated areas. Mismatch is highlighted in V/P_{quotient} images

19. INTERNAL RADIATION DOSIMETRY

The estimated absorbed radiation doses to an average ADULT patient (70 kg) from an intravenous injection of 148 MBq (4 mCi) of Tc-99m MAA are shown in Table below.

Absorbed Radiation Doses

Organs	mGy/148 MBq	rads/4 mCi
Total body	0.60	0.060
Lungs	8.8	0.88
Liver	0.72	0.072
Spleen	0.68	0.068
Kidneys	0.44	0.044
Bladder Wall		
2.0 hr. void	1.2	0.12
4.8 hr. void	2.2	0.22
Testes		
2.0 hr. void	0.24	0.024
4.8 hr. void	0.26	0.026
Ovaries		
2.0 hr. void	0.30	0.030
4.8 hr. void	0.34	0.034

In PEDIATRIC patients, the radiation absorbed doses using the maximum recommended dose for lung imaging are based on 1.85 MBq (50 µCi) per kilogram of body weight [except in the newborn where the maximum recommended dose of 18.5 MBq (500 µCi) is used] and are shown in Table below. Note the recommendations regarding number of particles to be administered.

Pediatric Radiation Dose from Tc 99m MAA for Lung Imaging*

Age	Newborn		1 year		5 years		10 years		15 years	
Weight (kg)	3.5		12.1		20.3		33.5		55.0	
Max. Recommended Dose in Megabecquerels and Millicuries	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi
	18.5	0.5	22.2	0.6	37	1.0	62.9	1.7	103.6	2.8
Range of Particles Administered	10-50,000		50-150,000		200-300,000		200-300,000		200-700,000	
Absorbed Radiation Dose in milliGreys and Rads for the Maximum Dose	mGy	Rads	mGy	Rads	mGy	Rads	mGy	Rads	mGy	Rads
ORGANS										
Total Body	0.60	0.06	0.30	0.03	0.31	0.031	0.48	0.048	0.41	0.041
Lungs	19.00	1.9	6.60	0.66	5.80	0.58	8.70	0.87	7.70	0.77
Liver	1.40	0.14	0.60	0.06	0.62	0.062	1.80	0.18	1.20	0.12
Bladder Wall	2.10	0.21(1)	1.50	0.15(1)	3.10	0.31(2)	3.90	0.39(2)	4.10	0.41
Ovaries	0.38	0.038	0.20	0.020	0.19	0.019	0.44	0.044	0.41	0.041
Testes	0.31	0.031	0.13	0.013	0.19	0.019	0.20	0.020	0.36	0.036