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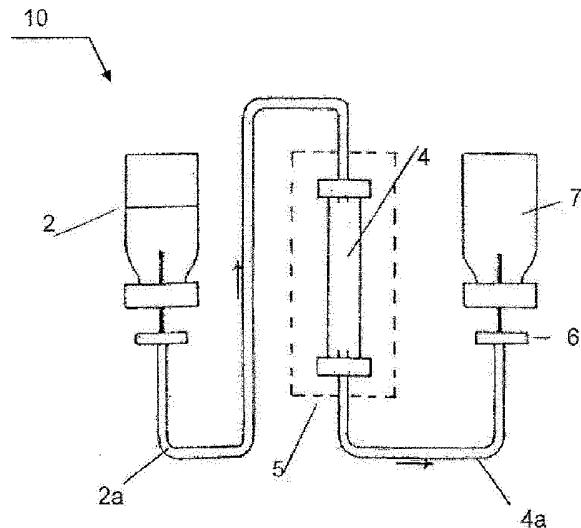
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(74) Gemachtigde:

ir. C.M. Jansen c.s. te Den Haag.

(54) A column material and a method for adsorbing Mo-99 in a 99Mo/99mTc generator.

(57) The invention relates to a column material for adsorbing Mo-99 in a ⁹⁹Mo/^{99m}Tc generator, said column material (4) comprising a mesoporous material. Preferably, a pore size of the mesoporous material is in the range of 1.5 -50 nm, preferably in the range of 2-30 nm. More preferably, the mesoporous material is selected from the group consisting of: Al₂O₃, TiO₂, Al₂O₃-SiO₂, TiO₂-SiO₂, MSU-A1, TUD1-A1. The invention further relates to a method for adsorbing Mo-99 in a ⁹⁹Mo/^{99m}Tc generator, a column (10) and use of a mesoporous material.



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Dit octrooi is verleend ongeacht het bijgevoegde resultaat van het onderzoek naar de stand van de techniek en schriftelijke opinie. Het octrooischrift komt overeen met de oorspronkelijk ingediende stukken.

P95495NL00

Title: A column material and a method for adsorbing Mo-99 in a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator

FIELD OF THE INVENTION

The invention relates to a column material for adsorbing Mo-99 in a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator.

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The invention still further relates to a column for adsorbing Mo-99 in a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator.

10 The invention further relates to a method for adsorbing Mo-99 in a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator.

The invention still further relates to use of a mesoporous material.

BACKGROUND OF THE INVENTION

15

An embodiment of a method as is set forth in the opening paragraph is known from US 5, 910, 971. In the known method a molybdenum-99 isotope is generated in the uranyl sulphate nuclear fuel of a homogeneous solution nuclear reactor. The 99-molybdenum isotope is extracted from the fuel by a solid polymer 20 sorbent. The sorbent is composed of a composite ether of a maleic anhydride copolymer and α -benzoin-oxime.

In the known method use is made of the following nuclear reaction for producing the molybdenum-99 isotope: $^{235}\text{U} \rightarrow ^{99}\text{Mo} \rightarrow ^{99\text{m}}\text{Tc}$. It is appreciated that 25 $^{99\text{m}}\text{Tc}$ is the isotope which has relevant clinical value for diagnostic purposes. However, $^{99\text{m}}\text{Tc}$ has a half-life time of about 6 hours which induces logistic problems associated with generation and delivery of ^{99}Mo obtained in the nuclear generator.

30 An embodiment of a column for production of Molybdenum-99 is known from RU 2 296 712. The known column is used in the nuclear aqueous solution reactor

wherein molybdenum-99 is being produced. The resulting molybdenum-99 is being sorbed in a column, washed off the sorbent material and subsequently desorbed and cleaned from radio-nuclides and chemical admixtures.

5 It is a disadvantage of the known column that complicated post-processing steps are required after the molybdenum-99 isotope has been adsorbed in the column.

A still further embodiment of a process and a device for producing molybdenum-99 is known from WO 2011/081576. In the known method and the device
10 use is made of a solution reactor wherein fuel comprising uranyl sulfate is used. After the nuclear reactor is brought into power the production of molybdenum-99 commences after which the produced molybdenum-99 is sorbed. For purposes of sorbing, the solution containing molybdenum-99 is being pumped through a column comprising a suitable sorbent after which the nuclear fuel may be conditioned and
15 reused.

It is a disadvantage of the known method that sorbing capacity of molybdenum-99 isotope in the known column is sub-optimal.

20 A still further method of generating $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ isotopes is known from US 4, 782, 231. In the know method use is made of a column comprising a molybdenum target which is subjected to a medium flux neutron irradiation. The resulting isotopes are produced by the following reaction: $^{98}\text{Mo}(\text{n}, \gamma) \rightarrow ^{99}\text{Mo}/^{99\text{m}}\text{Tc}$. The resulting $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ is eluted from the column using an elution solution of 0.9%
25 solution of NaCl by weight.

It is a disadvantage of the known method that at least there is a specific maximum to the Mo loading capacity. In addition, it is a disadvantage of the known method that the release efficiency of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ may be relatively low.

SUMMARY OF THE INVENTION

It is an object of the invention to provide an improved method of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generation. In particular, it is an object of the invention to provide an improved method of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generation wherein Mo adsorbing processes in a column are optimized followed by an efficient release of produced $^{99\text{m}}\text{Tc}$.

To this end in the column material for adsorbing Mo-99 in a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator, according to the invention, said column material comprises a mesoporous material.

It is found that when using a mesoporous material in the column, due to a large surface area of such material, it has a substantially increased capacity than the conventional materials based on Aluminum oxide.

15

Accordingly, much higher amounts of Mo can be loaded (adsorbed) in $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators without increasing the volume of the generator. Higher capacity of the generator column allows for the use of ^{99}Mo with much lower specific activity (SA) than compared to the devices known from the art. Accordingly, relaxed 20 constrained on SA means that the production of ^{99}Mo from natural molybdenum rather than from the enriched ^{98}Mo using a high neutron flux reactor can successfully replace ^{99}Mo obtained by fission of ^{235}U . Accordingly, not only the costs of the ^{99}Mo production may be decreased, but also a substantial contribution to the protection of the environment can be made.

25

The technical measure of the invention is based on the following insights. According to the practice as is known from the art, a specific quantity of ^{99}Mo radioactivity and a specific associated Mo mass is loaded onto a specific mass of column material, under specific conditions and procedural approaches, for purposes of 30 increasing loading efficiency. In addition, specific and complicated measures are undertaken in the prior art methods to avoid Mo breakthrough, and to achieve an efficient release of produced $^{99\text{m}}\text{Tc}$.

Accordingly, the known columns used for adsorption of molybdenum isotopes have to be tuned at least for meeting the following desirable criteria:

- 5 i) a specific maximum to the Mo loading capacity;
- ii) a specific optimum to the Mo column affinity
- iii) a minimum to the ^{99}Mo specific radioactivity (SA) to be applied;
- iv) a minimum to the column material mass to be used;
- v) a limited number of routes to produce ^{99}Mo of the required high SA;
- vi) a limited set of applicable conditions, dictated, for example by column solubility in an elution solution.

10

It has been found that the limited column Mo capacity (i) requires for a high ^{99}Mo SA (iii), the limited column Mo affinity (ii) may lead to Mo breakthrough incidences, and the overall need of large column mass (iv) implies the necessary large mass of radiation shielding to be implemented into the eventual generator lay-outs.

15 Furthermore, the needed high ^{99}Mo SA (iii) limits the available possibilities for production of ^{99}Mo (v), and experimental approaches and material choices should prevent any column solubility (vi).

20 Research has indicated that column materials of higher Mo capacity and affinity may permit more Mo to be loaded (i,ii), as well as may permit less column material to be used (iv) with smaller amount of necessary shielding. In addition such column materials may permit ^{99}Mo to be used of lower SA (iii), thereby increasing the production-possibilities for ^{99}Mo in ^{99}Mo - $^{99\text{m}}\text{Tc}$ generators. However, an additional feature of the column material should be that it has limited solubility under the 25 conditions of Mo loading and Tc unloading (vi).

30 It has been found that a material composed of or comprising a mesoporous material meets all above criteria and is particularly suitable to be used as a column material for generation $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ as is set forth in the foregoing.

30

In an embodiment of the column material according to the invention a pore size of the mesoporous material is in the range of 1.5 – 50 nm, preferably in the range of 2 – 30 nm.

It is further found that a material described in US 2006/0052234 is particularly suitable for embodying the column material.

5 In a further embodiment of the column material according to the invention, the mesoporous material is selected from the group consisting of: Al₂O₃, TiO₂, Al₂O₃-SiO₂, TiO₂-SiO₂, MSU-Al, TUD1-Al.

10 Experimental verification of said column properties is done both in batch approaches, in which column solids and Mo-solutions are mixed for specific mixing time, and in column set-ups, in which ⁹⁹Mo is loaded and capacity assessment is performed by subsequent elution of 0.9 % NaCl pH 7 solutions.

15 Tracking of column (material) properties towards Mo is done by data interpretation routines on Langmuir, Freundlich and other conventional saturation isotherms, thereby specifically giving insight in column Mo capacity and affinity. Basic equations used are the generalized Langmuir isotherm (Rill et al. Langmuir 25 (4),2294 (2009)):

$$20 \quad q_e = q_{\max} \left[\frac{(K \cdot c_e)^n}{1 + (K \cdot c_e)^n} \right]^{m/n} \quad (1)$$

with q_e as the adsorbed amount of Mo, c_e as the Mo concentration in solution, q_{max} as the saturation (maximum) column Mo loading, K as a constant, to be regarded as the affinity constant, and with m and n as surface heterogeneity parameters. For the 25 Langmuir model, m and n are both equal to 1, thereby giving

$$q_e = q_{\max} \frac{(K_L \cdot c_e)}{1 + (K_L \cdot c_e)} \quad (2)$$

With K_L as the Langmuir (adsorption equilibrium) constant. The Langmuir-Freundlich (LF) and Tóth models (T) assume that adsorption energy is not equal for all sites, as expressed by deviations of m and n from unit value. The Langmuir-Freundlich model assumes m=n (eq 3), the Tóth model assumes m=1, eq 4)

5

$$q_e = q_{\max} \frac{(K_{LF} \cdot c_e)^n}{1 + (K_{LF} \cdot c_e)^n} \quad (3)$$

or

$$q_e = q_{\max} \left[\frac{(K_T \cdot c_e)^n}{1 + (K_T \cdot c_e)^n} \right]^{1/n} \quad (4)$$

- 10 The Freundlich isotherm (F) is a further (empirical) model, with K_F as the Freundlich affinity constant (see eq 5), which does not limit the adsorption to a monolayer and is often applicable to adsorption on heterogeneous surfaces

$$q_e = K_F c_e^{1/n} \quad (5)$$

15

In addition, an adapted form of the extended Langmuir equation is used (Zhang P., Wang, L. Separation and Purification Technol. 70, 367-371, 2010), as

$$q_e = q_{\max} \left[\frac{K_L c_e}{1 + K_L c_e} \right] e^{\frac{n c_e}{c_{\max}}} \quad (6)$$

20

with $c_e \leq c_{\max}$ (c_{\max} representing e.g. c solubility, for Molybdates reported as ca 65 mg/L at 20 °C), and eq (6) reducing to eq (2) for n=0.

In experimental verification, mostly eqs 5 and 6 were used.

25

Column materials, in mixed or un-mixed forms were taken into batch experiments, in which various Mo compounds (e.g such as dissolved $(\text{NH}_4)_2\text{MoO}_4$, Na_2MoO_4 or MoO_3) and were loaded (adsorbed) onto said materials, under variable conditions viz. acidity (e.g. pH 2-8, see Table 2 for various Mo forms depending on 5 acidity), counter ions (e.g. Na^+ , NH_4^+), sorption duration, column pre-conditioning approaches (e.g. washing), and set ionic strength (by adding NaCl). Where considered necessary, all further experiments were performed in Na-acetate (0.15 M) buffered solutions.

10 Results on sorption time indicate that 10 min is enough to largely reach equilibrium in batches: accordingly all further batch tests were carried out with the 30 min duration to ensure full steady state. Results on Mo sorption for various sorber materials with varying NaCl concentrations show that Langmuir constants decrease with increasing ionic strength. Accordingly, it is found preferably to select the ionic 15 strengths to about 0.15 M.

In addition, a number of experiments are presented for pH 2-3, one using a large range of Mo concentrations (remaining far below Mo solubility values), to derive the column capacity q_m and formation constant K_L (eq 6), and the other one using a 20 Mo range, limited to small Mo concentrations, to derive an expression of affinity K_F (eq 5). The results indicate best performance (regarding both q_m and K_L) for MSU-X and TUD1-Al materials, with high Freundlich outcomes relative to conventional sorbers.

25 It will be appreciated that MSU-X (wormhole) is a commercially available mesoporous material (SIGMA-Aldrich 517747), with $S_{\text{BET}}=364 \text{ m}^2/\text{g}$, pore size = 3.8 nm average, particle size 5.65 μm on average.

The TUD1-Al material has $S_{\text{BET}}=428 \text{ m}^2/\text{g}$, pore volume = 0.832 cm^3/g , and 30 pore diameter 6.3 nm. It will be appreciated that the TUD1-Al material is developed and patented by the Applicant, see US 2006/0052234. For the sake of conciseness the disclosure of US 2006/0052234 is not recited here.

In addition to batch experiments, also column experiments were performed, in which ^{99}Mo was preloaded (pH 2) into a 2 g sorber column (column total volume 8 cm height by 0.8 cm Φ), after which extended elutions (up to 100 ml, pH 2, 0.9 % NaCl) were used to monitor column capacity. Results indicate 52.6 mg Mo/g column capacity for (acid y-)Al₂O₃ and 101.5 mg Mo/g column capacity for mesoporous Al₂O₃ (MSU-X), thereby fully substantiating the earlier obtained batch results.

Accordingly, it has been demonstrated that a column material composed of or comprising a mesoporous material as is set forth in the foregoing substantially improved adsorption properties of a column used for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generation.

The invention further relates to a column comprising the column material as is set forth in the foregoing. Preferably, the column is adapted to form part of an elution system. This embodiment will be discussed in more detail with reference to Figure 1.

The invention method of adsorbing Mo from a solution into a sorber material, wherein for the sorber material a mesoporous material is used. Preferably, the mesoporous material is selected from the group consisting of: Al₂O₃, TiO₂, Al₂O₃-SiO₂, TiO₂-SiO₂, MSU-Al, TUD1-Al.

In a further embodiment according to a further aspect of the invention the solution is acidic having pH in the range of 2 – 3.

In a still further embodiment of the method according to the invention an ionic strength of the solution is about 0.15 mol/L.

Use of a mesoporous material according to the invention is effectuated in a column arranged for adsorbing Mo-99 in a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator. Preferably, the mesoporous material having a pore size in the range of 1.5 – 50 nm, preferably in the range of 2 – 30 nm is used. More preferably, the mesoporous material is selected from the group consisting of: Al₂O₃, TiO₂, Al₂O₃-SiO₂, TiO₂-SiO₂, MSU-Al, TUD1-Al.

These and other aspects of the invention will be discussed with reference to drawings wherein like reference signs correspond to like elements. It will be appreciated that the drawings are presented for illustrative purposes only and may not be used for limiting the scope of the appended claims.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents in a schematic way an embodiment of a column provided with a mesoporous material, forming part of an elution system.

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DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1 presents in a schematic way an embodiment of a column 4 provided with a mesoporous material, forming part of an elution system 10. The column 4 is provided with a mesoporous material used for adsorbing ^{99}Mo isotopes. In accordance with the invention, the mesoporous material may be selected from a group consisting of Al_2O_3 , TiO_2 , $\text{Al}_2\text{O}_3\text{-SiO}_2$, $\text{TiO}_2\text{-SiO}_2$, MSU-Al, TUD1-Al. It will be appreciated that MSU-X (wormhole) is a commercially available mesoporous material (SIGMA-Aldrich 517747), with $S_{\text{BET}}=364 \text{ m}^2/\text{g}$, pore size = 3.8 nm average, particle size $5.65 \mu\text{m}$ average.

20

The TUD1-Al material has $S_{\text{BET}}=428 \text{ m}^2/\text{g}$, pore volume = $0.832 \text{ cm}^3/\text{g}$, and pore diameter 6.3 nm. It will be appreciated that the TUD1-Al material is developed and patented by the Applicant, see US 2006/0052234. For the sake of conciseness the disclosure of US 2006/0052234 incorporated herein by reference is not recited. In particular, paragraphs [0038] – [0061] are incorporated herewith by reference.

In accordance with the present embodiment, ^{99}Mo may be loaded in an alumina sorber and provided in the column 4. The elution vial 2 may be used for supplying a suitable elution liquid via the conduit 2a into the column 4. Preferably, the column 4 is suitably shielded against emanating radiation, for example using a lead shield 3.

The elution solution may comprise 0.9% NaCl, which may be fed into the column with a flow rate of 1 ml/min. The volume of the column 4 may be as large as 100 ml. The extracted solution may be collected in an extraction vessel 7 using an exit conduit 4a. Preferably, prior to the extraction vessel 7 a suitable filet 6 is arranged.

5

It will be appreciated that the above eluting scheme is exemplary, not limiting. Any other suitable elution scheme as known from the may be used. For example, the elution scheme known from US2011/0250107 may be used.

10

While specific embodiments have been described above, it will be appreciated that the invention may be practiced otherwise than as described. Moreover, specific items discussed with reference to any of the isolated drawings may freely be inter-changed supplementing each outer in any particular way. The descriptions above are intended to be illustrative, not limiting. Thus, it will be apparent to one skilled in the art that modifications may be made to the invention as described in the foregoing without departing from the scope of the claims set out below.

15

Conclusies

1. Kolommateriaal voor het adsorberen van Mo-99 in een $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator, het kolommateriaal omvattende een mesoporeus materiaal.
2. Kolommateriaal volgens conclusie 1, waarbij een poriegrootte van het mesoporeuze materiaal in het bereik van 1,5 – 50 nm ligt, bij voorkeur in het bereik van 2 – 30 nm.
3. Kolommateriaal volgens conclusie 1 of 2, waarbij het mesoporeuze materiaal is geselecteerd uit een groep bestaande uit: Al_2O_3 , TiO_2 , $\text{Al}_2\text{O}_3\text{-SiO}_2$, $\text{TiO}_2\text{-SiO}_2$, MSU-Al, TUD1-Al.
4. Kolom omvattende het kolommateriaal volgens één van de voorgaande conclusies.
5. Kolom volgens conclusie 1, geschikt om een deel van een elutiesysteem te vormen.
6. Werkwijze voor het in een sorptiemateriaal adsorberen van Mo uit een oplossing, waarbij als sorptiemateriaal een mesoporeus materiaal wordt gebruikt.
7. Werkwijze volgens conclusie 6, waarbij het mesoporeuze materiaal is geselecteerd uit een groep bestaande uit: Al_2O_3 , TiO_2 , $\text{Al}_2\text{O}_3\text{-SiO}_2$, $\text{TiO}_2\text{-SiO}_2$, MSU-Al, TUD1-Al.
8. Werkwijze volgens conclusie 6 of 7, waarbij de oplossing zuur is met een pH in het bereik van 2 – 3.
9. Werkwijze volgens conclusie 8, waarbij de ionsterkte van de oplossing rond 0,15 mol/L is.
10. Gebruik van een mesoporeus materiaal in een kolom voor het adsorberen van Mo-99 in een $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator.
11. Gebruik volgens conclusie 10, waarbij een poriegrootte van het mesoporeuze materiaal in het bereik van 1,5 – 50 nm ligt, bij voorkeur in het bereik van 2 – 30 nm.
12. Gebruik volgens conclusie 10 of 11, waarbij het mesoporeuze materiaal is geselecteerd uit een groep bestaande uit: Al_2O_3 , TiO_2 , $\text{Al}_2\text{O}_3\text{-SiO}_2$, $\text{TiO}_2\text{-SiO}_2$, MSU-Al, TUD1-Al.

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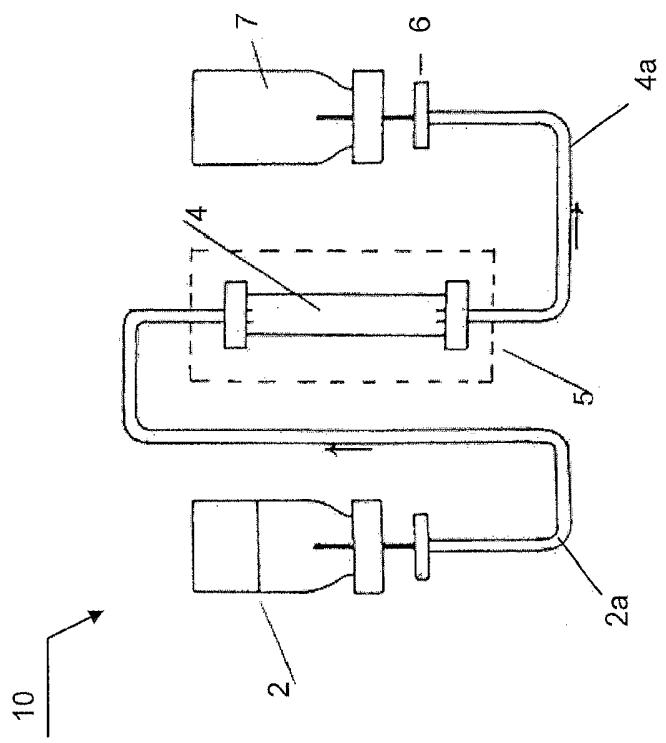


Fig. 1

SAMENWERKINGSVERDRAG (PCT)

RAPPORT BETREFFENDE NIEUWHEIDSONDERZOEK VAN INTERNATIONAAL TYPE

IDENTIFICATIE VAN DE NATIONALE AANVRAGE		KENMERK VAN DE AANVRAGER OF VAN DE GEMACHTIGDE
		P95495NL00
Nederlands aanvraag nr. 2007951	Indieningsdatum 12-12-2011	
	Ingeroepen voorrangsdatum	
Aanvrager (Naam) Technische Universiteit Delft		
Datum van het verzoek voor een onderzoek van internationaal type 10-03-2012	Door de Instantie voor Internationaal Onderzoek aan het verzoek voor een onderzoek van internationaal type toegekend nr. SN 57807	
I. CLASSIFICATIE VAN HET ONDERWERP (bij toepassing van verschillende classificaties, alle classificatiesymbolen opgeven) Volgens de internationale classificatie (IPC)		
B01J20/06 G21G1/00		B01J20/10
		B01J20/18
		G21G4/08
II. ONDERZOCHE GEBIEDEN VAN DE TECHNIEK Onderzochte minimumdocumentatie		
Classificatiesysteem	Classificatiesymbolen	
IPC	B01J	G21G
Onderzochte andere documentatie dan de minimum documentatie, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen		
III.	GEEN ONDERZOEK MOGELIJK VOOR BEPAALDE CONCLUSIES (opmerkingen op aanvullingsblad)	
IV.	GEBREK AAN EENHEID VAN UITVINDING (opmerkingen op aanvullingsblad)	

**ONDERZOEKSRAPPORT BETREFFENDE HET
RESULTAAT VAN HET ONDERZOEK NAAR DE STAND
VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE**

Nummer van het verzoek om een onderzoek naar de stand van de techniek NL 2007951
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<p>A. CLASSIFICATIE VAN HET ONDERWERP INV. B01J20/06 B01J20/10 B01J20/18 G21G4/08 G21G1/00 ADD.</p> <p>Volgens de Internationale Classificatie van octrooiën (IPC) of zowel volgens de nationale classificatie als volgens de IPC.</p> <p>B. ONDERZOCHE GEBIEDEN VAN DE TECHNIEK Onderzochte minimum documentatie (classificatie gevolgd door classificatiesymbolen) B01J G21G</p> <p>Onderzochte andere documentatie dan de minimum documentatie, voor dergelijke documenten, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen</p> <p>Tijdens het onderzoek geraadpleegde elektronische gegevensbestanden (naam van de gegevensbestanden en, waar uitvoerbaar, gebruikte trefwoorden) EPO-Internal, WPI Data</p>					
C. VAN BELANG GEACHTE DOCUMENTEN					
Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.			
X	<p>ASHUTOSH DASH ET AL: "Development of a Mo/Tc generator using alumina microspheres for industrial radiotracer applications", APPLIED RADIATION AND ISOTOPES, ELSEVIER, OXFORD, GB, deel 70, nr. 1, 21 juli 2011 (2011-07-21), bladzijden 51-58, XP028106345, ISSN: 0969-8043, DOI: 10.1016/J.APRADISO.2011.07.012 [gevonden op 2011-07-29]</p> <ul style="list-style-type: none"> * Abstract; bladzijde 51 * * bladzijde 53, rechter kolom - bladzijde 54, linker kolom * * figuur 1 * * 2.7. Development of 99Mo/99mTc generator; bladzijde 53, linker kolom * * 3.5. Sorption capacity of alumina <p>-/-</p>	1-12			
<input checked="" type="checkbox"/> Verdere documenten worden vermeld in het vervolg van vak C.		<input checked="" type="checkbox"/> Leden van dezelfde octrooifamilie zijn vermeld in een bijlage			
<p>° Speciale categorieën van aangehaalde documenten</p> <p>"A" niet tot de categorie X of Y behorende literatuur die de stand van de techniek beschrijft</p> <p>"D" in de octrooiaanvraag vermeld</p> <p>"E" eerdere octrooi(aanvraag), gepubliceerd op of na de indieningsdatum, waarin dezelfde uitvinding wordt beschreven</p> <p>"L" om andere redenen vermelde literatuur</p> <p>"O" niet-schriftelijke stand van de techniek</p> <p>"P" tussen de voorrangsdatum en de indieningsdatum gepubliceerde literatuur</p> <p>"X" na de indieningsdatum of de voorrangsdatum gepubliceerde literatuur die niet bewaard is voor de octrooiaanvraag, maar wordt vermeld ter verheldering van de theorie of het principe dat ten grondslag ligt aan de uitvinding</p> <p>"Y" de conclusie wordt als niet nieuw of niet inventief beschouwd ten opzichte van deze literatuur</p> <p>"*&" lid van dezelfde octrooifamilie of overeenkomstige octrooipublicatie</p>					
Datum waarop het onderzoek naar de stand van de techniek van internationaal type werd voltooid 7 augustus 2012		Verzenddatum van het rapport van het onderzoek naar de stand van de techniek van internationaal type			
Naam en adres van de instantie European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		De bevoegde ambtenaar Kaluza, Nicoleta			

**ONDERZOEKSRAPPORT BETREFFENDE HET
RESULTAAT VAN HET ONDERZOEK NAAR DE STAND
VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE**

Nummer van het verzoek om een onderzoek naar
de stand van de techniek
NL 2007951

C.(Vervolg). VAN BELANG GEACHTE DOCUMENTEN		
Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	<p>microspheres; bladzijde 54 *</p> <p>* tabellen 1-3 *</p> <p>* 3.8. Regeneration of the alumina column; bladzijde 56 *</p> <p>-----</p> <p>R.CHAKRAVARTY, R. SHUKLA, S. GANDHI, R. RAM, A. DASH, M. VENKATESH AND A.K. TYAGI: "Polymer Embedded nanocrystalline Titania Sorbent for 99Mo-99mTc Generator", JOURNAL OF NANOSCIENCE AND NANOTECHNOLOGY, deel 8, nr. 9, 1 september 2008 (2008-09-01), bladzijden 4447-4452, XP008154346, USA DOI: 10.1166/jnn.2008.280</p> <p>* Abstract; bladzijde 4447 *</p> <p>* 2.1. Synthesis of the Titanium Polymer Adsorbent (TiP); bladzijde 4448, linker kolom *</p> <p>* 2.3. Application of TiP in Preparation of 99Mo-99mTc Generator; bladzijde 4448, linker kolom - bladzijde 4449, linker kolom *</p> <p>* 3.2. Structural Investigation; bladzijde 4449, linker kolom - bladzijde 4450, linker kolom *</p> <p>* 3.3. Application of Polymer Embedded Nano-Cristalline Titania Sorbent in 99Mo-99mTc Generator; bladzijde 4450, linker kolom - bladzijde 4451, rechter kolom *</p> <p>-----</p> <p>WO 2011/106847 A1 (AUSTRALIAN NUCLEAR SCIENCE TEC [AU]; LE VAN SO [AU]) 9 september 2011 (2011-09-09)</p> <p>* conclusies 1-5, 23, 26-32 *</p> <p>* bladzijde 13, regel 1 - regel 20 *</p> <p>* bladzijde 11, regel 32 - regel 34 *</p> <p>-----</p> <p>WO 01/53205 A1 (TCI [US]) 26 juli 2001 (2001-07-26)</p> <p>* conclusies 1,3 *</p> <p>-----</p>	1-12
X		1-9
		-/-

**ONDERZOEKSRAPPORT BETREFFENDE HET
RESULTAAT VAN HET ONDERZOEK NAAR DE STAND
VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE**

Nummer van het verzoek om een onderzoek naar
de stand van de techniek
NL 2007951

C.(Vervolg). VAN BELANG GEACHTE DOCUMENTEN		
Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	SELVEDIN TELALOVIC ET AL: "TUD-1: synthesis and application of a versatile catalyst, carrier, material...", JOURNAL OF MATERIALS CHEMISTRY, deel 20, nr. 4, 28 augustus 2009 (2009-08-28), bladzijde 642, XP55034772, ISSN: 0959-9428, DOI: 10.1039/b904193a * bladzijde 642, linker kolom * * Scheme 1 * * bladzijde 643, linker kolom * * tabel 1 * -----	1-5
X,D	US 2006/052234 A1 (SHAN ZHIPING [US] ET AL) 9 maart 2006 (2006-03-09) in de aanvraag genoemd * alinea [0038] - alinea [0044] * * alinea [0055] * -----	1-5
X	US 2011/105300 A1 (CHAUMONNOT ALEXANDRA [FR] ET AL) 5 mei 2011 (2011-05-05) * conclusies 1-10,15 * * alinea [0032] * -----	1-5
X	US 6 129 904 A (VON THIENEN NORBERT [DE] ET AL) 10 oktober 2000 (2000-10-10) * conclusies 1,2 * * kolom 1, regel 3 - regel 5 * -----	1-5

**ONDERZOEKSRAPPORT BETREFFENDE HET
RESULTAAT VAN HET ONDERZOEK NAAR DE STAND
VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE**

Informatie over leden van dezelfde octrooifamilie

Nummer van het verzoek om een onderzoek naar
de stand van de techniek

NL 2007951

In het rapport genoemd octrooigeschrift	Datum van publicatie	Overeenkomend(e) geschrift(en)		Datum van publicatie
WO 2011106847	A1	09-09-2011	GEEN	
WO 0153205	A1	26-07-2001	AU 774552 B2 AU 3595400 A CA 2390790 A1 EP 1324951 A1 JP 2003529517 A US 6337055 B1 WO 0153205 A1	01-07-2004 31-07-2001 26-07-2001 09-07-2003 07-10-2003 08-01-2002 26-07-2001
US 2006052234	A1	09-03-2006	GEEN	
US 2011105300	A1	05-05-2011	AT 556989 T CN 101980961 A DK 2274237 T3 EP 2274237 A2 FR 2929265 A1 JP 2011518101 A US 2011105300 A1 WO 2009122022 A2	15-05-2012 23-02-2011 25-06-2012 19-01-2011 02-10-2009 23-06-2011 05-05-2011 08-10-2009
US 6129904	A	10-10-2000	US 6129904 A US 6261533 B1	10-10-2000 17-07-2001



Agentschap NL
Ministerie van Economische Zaken,
Landbouw en Innovatie

WRITTEN OPINION

File No. SN57807	Filing date (day/month/year) 12.12.2011	Priority date (day/month/year)	Application No. NL2007951
International Patent Classification (IPC) INV. B01J20/06 B01J20/10 B01J20/18 G21G4/08 G21G1/00			
Applicant Technische Universiteit Delft			

This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the application
- Box No. VIII Certain observations on the application

	Examiner Kaluza, Nicoleta
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WRITTEN OPINION**Box No. I Basis of this opinion**

1. This opinion has been established on the basis of the latest set of claims filed before the start of the search.
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - on paper
 - in electronic form
 - c. time of filing/furnishing:
 - contained in the application as filed.
 - filed together with the application in electronic form.
 - furnished subsequently for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes: Claims	
	No: Claims	1-12
Inventive step	Yes: Claims	
	No: Claims	1-12
Industrial applicability	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION

Box No. VII Certain defects in the application

see separate sheet

Box No. VIII Certain observations on the application

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

- D1 ASHUTOSH DASH ET AL: "Development of a Mo/Tc generator using alumina microspheres for industrial radiotracer applications", APPLIED RADIATION AND ISOTOPES, ELSEVIER, OXFORD, GB, deel 70, nr. 1, 21 juli 2011 (2011-07-21), bladzijden 51-58, XP028106345, ISSN: 0969-8043, DOI: 10.1016/J.APRADISO.2011.07.012 [gevonden op 2011-07-29]
- D2 R.CHAKRAVARTY, R. SHUKLA, S. GANDHI, R. RAM, A. DASH, M. VENKATESH AND A.K. TYAGI: "Polymer Embedded nanocrystalline Titania Sorbent for 99Mo-99mTc Generator", JOURNAL OF NANOSCIENCE AND NANOTECHNOLOGY, deel 8, nr. 9, 1 september 2008 (2008-09-01), bladzijden 4447-4452, XP008154346, USA, DOI: 10.1166/jnn.2008.280
- D3 WO 2011/106847 A1 (AUSTRALIAN NUCLEAR SCIENCE TEC [AU]; LE VAN SO [AU]) 9 september 2011 (2011-09-09)
- D4 WO 01/53205 A1 (TCI [US]) 26 juli 2001 (2001-07-26)
- D5 SELVEDIN TELALOVIC ET AL: "TUD-1: synthesis and application of a versatile catalyst, carrier, material...", JOURNAL OF MATERIALS CHEMISTRY, deel 20, nr. 4, 28 augustus 2009 (2009-08-28), bladzijde 642, XP55034772, ISSN: 0959-9428, DOI: 10.1039/b904193a
- D6 US 2006/052234 A1 (SHAN ZHIPING [US] ET AL) 9 maart 2006 (2006-03-09)in de aanvraag genoemd
- D7 US 2011/105300 A1 (CHAUMONNOT ALEXANDRA [FR] ET AL) 5 mei 2011 (2011-05-05)
- D8 US 6 129 904 A (VON THIENEN NORBERT [DE] ET AL) 10 oktober 2000 (2000-10-10)

Document D6 (US 2006/0522349) has been cited by the applicant in the description.

2 Furthermore, the mentioned lack of clarity notwithstanding (see **Item VIII** below), the subject-matter of claims 1, 6 and 10 is not new, and the criteria of patentability are therefore not met.

2.1 Document D1 discloses a chromatographic $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator for industrial applications using alumina microspheres synthesized through sol-gel process. The sorbent was mesoporous, mechanically strong and possesses high surface area (D1, page 51, Abstract). The alumina microspheres were prepared and characterized from structural point of view: density was in the range of 1,5-1,9 g/cm³, surface area measured by standard BET technique was found to be 175 m²/g and the pore size was determined based on BJH theory. The pores are in the range of 20-200 Å in sizes with predominant pore size 20-30 Å and an average pore size of 55 Å which lead to the conclusion that the obtained alumina is mesoporous and the long-range mesopores are distributed through out the structure (D1, page 53, right-hand column - page 54, left-hand column, Fig. 1). This alumina material was employed in a column for adsorbing ^{99}Mo in a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator (D1, page 53, left-hand column, 2.7. *Development of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator*). The sorption capacity of alumina microspheres for ^{99}Mo was determined in both static and dynamic conditions (D1, page 54, 3.5. *Sorption capacity of alumina microspheres*, Tables 1-3). The separated $^{99\text{m}}\text{Tc}$ was qualitatively controlled by investigating the radionuclidic purity and the radiochemical purity and its chemical purity. Furthermore, the alumina microspheres may be regenerated by treatment with NaOH and H₂O₂ (D1, page 56, 3.8. *Regeneration of the alumina column*).

In view of D1, the subject-matter of claims 1, 6 and 10 is not new.

2.2 Document D2 discloses a polymer embedded nanocrystalline titania sorbent for a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator (D2, page 4447, Abstract). In D2, the preparation of the sorbent is described (D2, page 4448, left-hand column, 2.1. Synthesis of the Titanium Polymer Adsorbent (TiP) as well as its structural characterization (D2, pages 4449, left-hand column, -page 4450, left-hand column, 3.2. Structural investigation)). It was found that the surface area of the prepared composite by BET technique was 30 m²/g and after decomposing the polymer matrix, the surface area was 38 m²/g. The average pore size of the powder was found to be 4 Å, corresponding to 40 nm. Hence, the sorbent of D2 is a mesoporous material. The sorbent is employed in the fabrication of a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator (D2, page 4448, left-column-page 4449, right hand column, 2.3. Application of TiP in Preparation of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator and page 4450, left-hand column- page 4451, right-hand column, 33. Application of Polymer Embedded Nano-Crystalline Titania Sorbent in $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator). The absorbing capacity was determined in by batch method or dynamic method and the sorbent was packed in a glass column.

In view of D2, the subject-matter of claims 1, 6 and 10 is not new.

2.3 Document D3 discloses a sorbent for sorbing radioactive ions. The sorbent comprises a porous crystalline powder if a metal oxide or mixed metal oxide of transition metals such as Zr, Ti, Sn and Ge (D3, claims 1-4). The particle diameter of the sorbent is between 10 and 200 microns (D3, claim 5). the sorbent may be employed in a separation column for separating a first ion from a second ion (D3, claim 23) or in a generator (D3, claims 26-32). The sorbent of D3 may be porous, which it is equivalent with the fact that the mean pore size may be between 10 and 200 nm with a pore size distribution broad or narrow. The sorbent may exhibit mesopores with a mean diameter between 2 and 50 nm (D3, page 13, lines 1-20). While in D3 the sorbent is suitable in a ⁶⁸Ga generator, it may be also useful in other nuclide generators, for example in a ⁹⁹Mo/^{99m}Tc generator (D3, page 11, lines 32-34).

In view of D3, the subject-matter of claims 1, 6 and 10 is not new.

2.4 Document D4 also discloses a composition suitable to sorb molybdenum-99 form the fission by-products of a uranyl sulfate homogeneous-solution nuclear reactor, the sorbent comprising titanium dioxide and zirconium hydroxide in a pellet form of 0.1 to 2 mm in size and a specific surface area of 100 to 350 m²/g and having a mechanical strength of at least 15 MPa (D4, claim 1). The method of extracting Mo is also claimed (D4, claim 3).

Although in D4 is not explicitly mentioned that the sorbent is a mesoporous material, the sorbent exhibit high values of specific surface area and it may be considered that the sorbent will also possess mesopores.

In view of D4, the subject-matter of claims 1 and 6 is not new.

2.5 Furthermore, all cited documents D5-D8 discloses mesoporous materials which will be suitable to be employed in a column material for adsorbing Mo-99. Document D5 discloses TUD-1 as mesoporous silicate material (D5, page 642, left-hand column, page 644, Scheme 1). The TUD-1 material has pores diameters between 5 and 20 nm, surface area between 500 and 1000 m²/g and pore volumes of 0.6 to 1.7 cm³/g (D5, page 643, left-hand column). Different metal containing siliceous TUD-1 materials may also be synthesized , such as Al-TUD-1 (D5, Table 1).

Also document D6 discloses mesoporous materials (D6, [0038]-[0044]). In D6 is mentioned that the mesoporous materials may be employed as adsorbents (D6, [0055]).

Document D7 discloses mesostructured aluminosilicates materials with spherical particles of specific size (D7, claims 1-10) which may be employed as adsorbent (D7, claim 15, [0032]).

Document D8 discloses aluminium oxide composition with very narrow pore size distribution, with at least about 90% of the pore radii between 1.7 and 2.2 nm and a specific surface area equal or greater than 70 m²/g (D8, claim 1) or even compositions with a specific surface area equal to or greater than 100 m²/g and about 955 or more of the pore radii between 1.8 and 2.1 nm (D7, claim 2). The materials may be particularly suited to produce adsorption agents (D8, column 1, lines 3-5).

In view of D5-D8, the subject-matter of claim 1 is not new.

- 3 Dependent claims 2-5, 7-9, 11 and 12 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of novelty and/or inventive step.

Re Item VII

Certain defects in the application

- 4 On page 7, line 4 of the description, reference is made to Table 2 but no table could be found in the entire description.

Re Item VIII

Certain observations on the application

- 5 Independent claims 1, 6 and 10 are not clear.
- 5.1 Claim 1 is directed to an entity, namely " a column material" which is comprising a mesoporous material for a particular use, namely " for absorbing Mo-99 in a ⁹⁹Mo/^{99m}Tc generator". A claim to a substance or composition for a particular use should generally be construed as meaning a substance or composition which is fact suitable for the stated use; a known product which *prima facie* is the same as the substance or the composition defined in the claim, but which is in a form which would render it unsuitable for the stated use, would not deprive the claim of novelty, but if the known product is in a form in which it is in fact suitable for the stated use, though it has never been described for that use, it would deprive the claim of novelty.
- 5.2 Claim 1 is not supported by the description, as its scope is broader than justified by the description and drawings. In claim 1 is stated that the material contained in the column is a "mesoporous material". As drafted, may be interpreted that **any** mesoporous material could be used for adsorbing Mo-99, but in the description, only few materials are mentioned, such as Al₂O₃, TiO₂, Al₂O₃-SiO₂, TiO₂-SiO₂, MSU-Al, TUD1-Al (page 5, lines 5-7). Therefore, it is considered that claim 1 is supported by the description only for these materials.

- 5.3 The terms MSU-Al and TUD1-Al used in the description and in claims 3, 7 and 12 are vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear. It is not clear which is the chemical nature of the mentioned materials.
- 5.4 Also, for the materials denoted $\text{Al}_2\text{O}_3\text{-SiO}_2$ and $\text{TiO}_2\text{-SiO}_2$, there is not clear how the composition of the materials should be interpreted: if the materials should contain a mixture of the two components or between them there is a chemical interaction, such as existent in aluminosilicates or titanium silicates.
- 5.5 Although claims 6 and 10 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. Both claims are activity claims referring to adsorption of Mo into a mesoporous material. The aforementioned claims therefore lack conciseness.
- 5.6 The expression "incorporated by reference" (see for example page 9, line 25) and similar expressions, should be deleted from the description. If the applicant is of the opinion that the documents to which these expressions refer are of importance for understanding the present invention, then these documents should be briefly summarised in an objective way.