From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

AERA A/S
Niels Hemmingsens Gade 10, 5th floor
1153 Copenhagen K
DANEMARK

Date of mailing *(day/month/year)*
09 April 2021 (09.04.2021)

Applicant's or agent's file reference
P2601WO00

IMPORTANT NOTIFICATION

International application No.
PCT/EP2020/084701

International filing date *(day/month/year)*
04 December 2020 (04.12.2020)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
AERA A/S
Niels Hemmingsens Gade 10, 5th floor
1153 Copenhagen K
DENMARK

State of Nationality:
State of Residence:
Telephone No.: +4526166900
Facsimile No.:
E-mail address: admin@aera-ip.com
☒ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
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PTO-1390 (10-20)
Approved for use through 10/31/2022. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

Attorney Docket No.	
AERA001.005APC	
U.S. Application No. (if known, see 37 CFR 1.5)	

International Application No.	International Filing Date	Priority Date Claimed
PCT/EP2020/084701	December 4, 2020	December 5, 2019

Title of Invention
PRODUCTION OF HIGHLY PURIFIED 212PB

First Named Inventor
Roy H. Larsen

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.
2. ■ A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).
3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. ☐ is attached.
   b. ☐ was previously filed in the international phase under PCT Rule 4.17(iv).

Items 5 to 8 below concern amendments made in the international phase.

PCT Article 19 and 34 amendments

5. ☐ Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).
6. ☐ English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).
7. ☐ English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. ☐ Do not enter the amendment made in the international phase under PCT Article 19.

8b. ☐ Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

The following items 9 to 17 concern a document(s) or information included.

9. ■ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ■ A preliminary amendment.
11. ■ An Application Data Sheet under 37 CFR 1.76.
12. ☐ A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).
13. ☐ A power of attorney and/or change of address letter.
14. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825 (not required if sequence listing in text format was indicated on the PCT Request as part of the International Application and the sequence listing was published as part of the international application).
15. ☐ Assignment papers *(cover sheet and document(s))*. Name of Assignee: _____
16. ☐ 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

U.S. APPLN. No. (if known – see 37 CFR 1.5)	INTERNATIONAL APPLICATION No.	ATTORNEY DOCKET No.
	PCT/EP2020/084701	AERA001.005APC

17. ■ Other items or information:

International Search Report;
Written Opinion;
PCT/IB/304; PCT/IB/306; PCT/IB/308

The following fees have been submitted.	CALCULATIONS
18. ■ Basic national fee (37 CFR 1.492(a)) **$320**	$ 320
19. ■ Examination fee (37 CFR 1.492(c)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • All other situations **$800**	$ 800
20. ■ Search fee (37 CFR 1.492(b)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$140** • International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB..... **$540** • All other situations **$700**	$ 540
TOTAL OF 18, 19, and 20 =	$ 1660
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). Fee for each additional 50 sheets of paper or fraction thereof **$420**	$

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round **up** to a whole number)	RATE
- 100 =	/ 50 =		x **$420**

Surcharge for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h))..... **$160**	$ 160

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	38 - 20 =	18	x **$100**	$ 1800
Independent claims	- 3 =		x **$480**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+ $860**	$

Fee for submission of Sequence Listing text file of 300 MB to 800 MB (37 CFR 1.21(o)(1))..... **$1,060**	$
Fee for submission of Sequence Listing text file of more than 800 MB (37 CFR 1.21(o)(2))..... **$10,500**	$
Processing fee for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i))..... **$140 +**	$
TOTAL OF ABOVE CALCULATIONS =	$ 3620
■ **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½.	
☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent.	
TOTAL NATIONAL FEE =	$ 1810
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31)..... **$50.00** per property **+**	$
TOTAL FEES ENCLOSED =	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. ☐ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. _____ as follows:

i. ☐ any required fee.

ii. ☐ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ☒ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended to pay fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013, and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE 1: By providing this statement under 37 CFR 1.55 or 1.78, **this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA**.

NOTE 2: A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

Correspondence Address

☒ The address associated with Customer Number: 20995 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone			
Email					

Signature	/Eric Furman/	Date	June 2, 2022
Name (Print/Type)	Eric S. Furman	Registration No. (Attorney/Agent)	45664

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PRELIMINARY AMENDMENT

First Inventor: Roy H. Larsen	**Conf. No.:** Unassigned
App. No.: Unassigned	**Filed:** Herewith
Examiner: Unassigned	**Art Unit:** Unassigned
Title: PRODUCTION OF HIGHLY PURIFIED 212PB	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Prior to examination of the above-referenced application, please enter the following amendments and remarks.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks begin on page 8 of this paper.

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AMENDMENTS TO THE SPECIFICATION

Please insert the following heading and paragraph on page 1, line 2 of the specification:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Phase Application of PCT International Application Number PCT/EP2020/084701, filed on December 4, 2020, designating the United States of America and published in the English language, which is an International Application of and claims the benefit of priority to European Patent Application No. 19213759.4, filed on December 5, 2019, and European Patent Application No. 20172038.0, filed on April 29, 2020. The disclosures of the above-referenced applications are hereby expressly incorporated by reference in their entireties.

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AMENDMENTS TO THE CLAIMS

1. **(Currently Amended)** A method for obtaining a container comprising ^{212}Pb on the walls comprising ~~the steps of~~:

- providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source,
- connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided,
- allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, and/or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly,
- removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and
- obtaining a container comprising ^{212}Pb on an inner wall of the container and <u>being</u> substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

2-38. **(Cancelled)**.

39. **(New)** An assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

40. **(New)** A single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

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41. **(New)** The method according to claim 1, wherein the single chamber container assembly is gas tight.

42. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

43. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

44. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

45. **(New)** The method according to claim 1, wherein the ^{212}Pb activity is 0% to 114% of the ^{224}Ra precursor activity.

46. **(New)** The method according to claim 1, wherein the ^{212}Pb activity is 0% to 103% of the ^{228}Th precursor activity.

47. **(New)** The method according to claim 1, wherein the total amount of radioactivity in the single chamber container assembly is 1 kBq – 100 GBq.

48. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt.

49. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is bound to a non-radioactive material.

50. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution.

51. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

52. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere that is made of a material suitable for application of a liquid.

53. **(New)** The method according to claim 1, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere, which is made of material that is selected from the group consisting of quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibres and synthetic fibres.

54. **(New)** The method according to claim 53, wherein a strip or sphere is attached to the second part, which comprises a holder configured to retain the sponge, the wool, the strip or the sphere.

55. **(New)** The method according to claim 54, wherein the second part comprises a syringe, or wherein the holder is a syringe.

56. **(New)** The method according to claim 55, wherein the tip of the syringe has been pushed through a rubber cap.

57. **(New)** The method according to claim 1, wherein the second part comprises a rod that is attached to the closure of the container.

58. **(New)** The method according to claim 57, wherein the closure for the container is a cap, cover or a lid.

59. **(New)** The method according to claim 58, wherein the cap, cover or a lid is made of a material selected from the group consisting of quartz, glass, mineral, rubber, glass, paper, plastic, metal, ceramic, natural fibres or synthetic fibres.

60. **(New)** The method according to claim 59, wherein the ^{212}Pb precursor isotope source is placed on or in a sphere, configured to hold the source but allow radon diffusion.

61. **(New)** The method according to claim 1, wherein the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

62. **(New)** The method according to claim 61, wherein the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

63. **(New)** The method according to claim 1, wherein the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

64. **(New)** The method according to claim 1, wherein volume of the container is 1 µl to 10 litres.

65. **(New)** The method according to claim 1, wherein the amount of ^{212}Pb precursor isotope source on the inner wall of the container is less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source as measured as % relative radioactivity.

66. **(New)** The method according to claim 1, wherein the inner walls of the container are coated.

67. **(New)** The method according to claim 1, wherein the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

68. **(New)** The method according to claim 1, wherein the inner walls of the container are coated with a chelator, which is TCMC or a variant hereof.

69. **(New)** The method according to claim 1, wherein the container comprises an aqueous or an oil solution.

70. **(New)** The method according to claim 1, wherein the second part of the assembly comprises a piston that can be in open and closed positions.

71. **(New)** The method according to claim 1, wherein the second part of the assembly comprises a chamber with a gas tight o-ring seal.

72. **(New)** The method according to claim 1, wherein the second part of the assembly comprises a gas and liquid tight lid or valve.

73. **(New)** The method according to claim 1, wherein the assembly is made by a glass flask placed up-side down and with quartz wool with ^{224}Ra or ^{228}Th placed in the centre of the inside of the cap.

74. **(New)** A method of obtaining a ^{212}Pb solution comprising obtaining a container or assembly comprising ^{212}Pb on the walls according to claim 1, and subsequently collect the ^{212}Pb in a solution.

75. **(New)** A method of obtaining a ^{212}Pb solution comprising obtaining a glass flask assembly according to claim 73, unscrewing the flask standing up-side down from the cap with the source, and thereafter washing the interior of the flask with a solution to dissolve ^{212}Pb.

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REMARKS

The specification has been amended to recite the claims to priority and to cross-reference related applications. Claim 1 has been amended to better clarify the invention. Claims 2-38 have been cancelled without prejudice or disclaimer in favor of new claims 39-75. Accordingly, no new matter has been introduced by these amendments. Please conduct National Phase processing immediately.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 2, 2022

By: /Eric Furman/
Eric S. Furman, Ph.D., J.D.
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(30) Priority: **10.07.90 US 550468**

(43) Date of publication of application:
15.01.92 Bulletin 92/03

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(54) **Method and generator for producing radioactive Lead-212.**

(57) A method and generator for preparing the radioisotope of lead, ^{212}Pb, whereby ^{228}Th, in a closed chamber, is allowed to decay to gaseous ^{220}Rn which is then readily separated from the thorium and other decay products by diffusing the ^{220}Rn gas into a second chamber, where it decays to ^{212}Pb which can then be collected from the second chamber. The ^{228}Th preferably is amorphous, such as thorium stearate. Collection of ^{212}Pb occurs in a medium of high and open porosity into which the ^{220}Rn diffuses so that the decay products recoil into the medium. The ^{212}Pb can be recovered from this medium by dissolving the medium or by reacting it with an antibody-chelating complex solution to entrap it in the antibody-chelating complex.

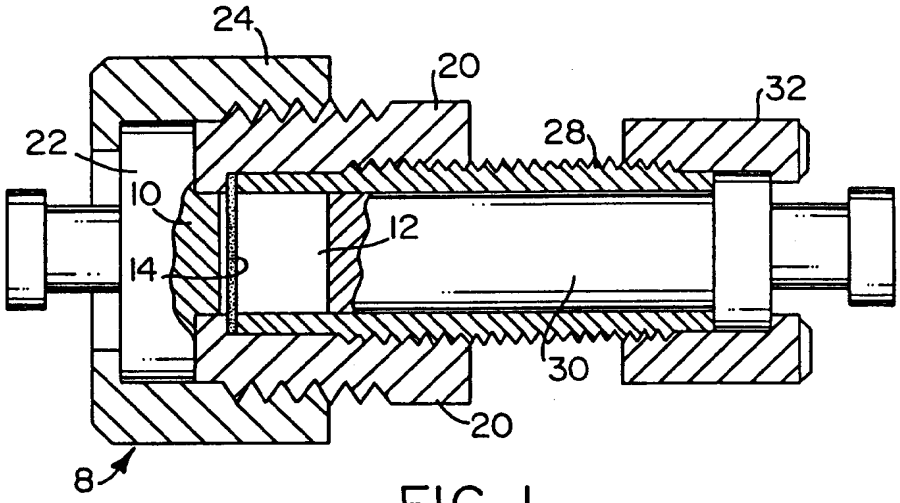


FIG. 1

EP 0 466 290 A1

This invention relates generally to the production and isolation of radioisotopes and more particularly to a method and generator for producing lead 212 (^{212}Pb) from thorium-228 (^{228}Th).

BACKGROUND OF THE INVENTION

Radioactive isotopes have a variety of applications. The choice of an appropriate isotope for any particular use depends on such factors as its half life and the type and energy of the radiation produced. The usefulness of certain isotopes may, however, be severly curtailed by the difficulty of their production and isolation.

Radiation therapy has long been used in the treatment of cancer and other localized lesions. The development of monoclonal antibodies, which can be targeted to specific cells with a high degree of specificity, has made it possible to selectively deliver radioactive agents predominantly to specifically targeted cells. The choice of an appropriate radioactive isotope is the critical aspect in targeting radiation therapy. An appropriate radioactive isotope should, desirably, have a half life which is long enough to permit any necessary logistic and pharmaceutical operations (transport, reaction, sterilization, etc.) prior to administration and arrival at the targeted cell after administration, without much loss of activity and damage in route, but is short enough so that therapeutic action proceeds rapidly. Generally one also desires radiation which is highly cytotoxic at short range so that the cell to which the antibody is attached is killed (as well as immediately adjacent cells that are likely to be also pathogenic) but harmless over longer distances so as not to injure healthy surrounding tissue. Absence of harmful persistent residues is also important.

Many potential radioactive candidates require a cyclotron for production and cannot be seriously considered for regular therapeutic use because of cost and availability reason. Of those possible candidates that do not need to be produced in a cyclotron, ^{212}Bi and ^{212}Pb have received considerable attention because they have acceptable decay form, energy, and half life characteristics.

While methods for producing both ^{212}Bi and ^{212}Pb are known, most require the use of complex equipment having a rather short life span. One less complicated, long lived generator for producing both ^{212}Bi and ^{212}Pb is shown in the literature by Zucchini et al., Intl. J. Nucl. Med. & Bio., Vol. 9, pp. 83 to 84 (June 1982). To produce ^{212}Pb in this generator, a bed of sodium titanate is maintained in a quarts column in which ^{228}Th in the tetravalent state and radium-224 (^{224}Ra) can be adsorbed above a coarse fritted glass disk sealed in the column. When water is passed through the titanate, ^{220}Rn, which is a decay product of ^{224}Ra, dissolves in the water. The water containing the ^{220}Rn passes through the fritted disk and is collected in a glass reservoir containing 2 cc of water therebelow. Since substantially all of the ^{220}Rn decays within 5 minutes in the water to ^{212}Pb, this provides sufficient delay. The water containing the ^{220}Rn is passed from the reservoir into a column containing a strongly acidic ion exchange resin, such as Bio-Rad AG-50 WX18 cation exchange resin (Bio-Rad, Richmond, CA), which adsorbs ^{212}Pb as the water passes through the column. After sufficient ^{212}Pb has been absorbed, the resin column is removed and the ^{212}Pb eluted therefrom using 2N HC1 to convert the lead isotope to $PbC1_3$. However, residual radioactivity and contamination was reported when this procedure was used, apparently due to a small amount of ^{228}Th and ^{224}Ra eluted. To reduce the contamination an additional ion exchange treatment is required.

There thus exists a need to provide an apparatus and method by which certain useful radioactive isotopes can be efficiently and safely produced. The present invention satisfies this need and provides related advantages as well.

SUMMARY OF THE INVENTION

The present invention provides a method and apparatus for producing radioisotopes which are formed as decay products from rare gases, which are in turn decay products of an element which can be immobilized.

The invention provides a method of obtaining daughter isotopes produced from the decay of a parent isotope via a rare gas intermediary by providing the parent isotope in gaseous contact with a gas permeable barrier impervious to the parent isotope, permitting gaseous intermediary isotopes to diffuse through the gas permeable barrier into a receiving chamber containing an open porosity porous medium, maintaining the gaseous intermediary the open porosity porous medium for a time sufficient to permit at least a portion of the rare gas intermediaries to decay into the daughter isotopes which recoil into and are captured by the open porosity porous medium and recovering from the open porosity porous medium a material whose principal radioactivity is that of the daughter isotopes. A generator for performing the process is also provided.

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In one embodiment, the parent isotope is ^{228}Th from which the daughter is ^{212}Pb. The open porosity medium can be, for example, urea, glucose, inorganic salts, lyophilized antibody or microspheres.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a sectional view of a diffusion generator as may be utilized in the practice of the process of the present invention.

Figure 2 is a sectional view of an alternate embodiment of the generator as can be utilized in a preferred practice of the process of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

This invention is directed to a simple and inexpensive process and a generator for producing radioactive isotopes which is rapid, simple and substantially free of contamination. An important advantage of the generator of this invention is that the parent isotope, which may be highly radioactive and difficult to handle and long lived, is contained in a parental chamber from which only the short lived radon isotope can readily escape. On the other hand, the receiving chamber can be readily loaded with the open porosity porous medium and the latter readily recovered therefrom when desired. Thus the generator can be loaded with the parent isotope in a facility adapted to handle high radiation levels and then transported and used for a long time at a hospital or radio-pharmacy where only the open porosity medium needs to be handled.

In one embodiment, the process and generator of the present invention involve the decay of a parent isotope, such as ^{228}Th, within a first closed chamber to yield a gaseous decay product, such as ^{220}Rn, and then allowing the gaseous decay product to diffuse to a second closed receiving chamber, thereby effectively separating the gaseous decay product from the parent and from other solid decay products. The second closed chamber contains an open porosity porous medium, which can be water soluble, such as a bed of powdered urea or sucrose, into the open porosity of which the radon can diffuse. Decay of ^{220}Rn to ^{212}Pb (via very short lived polonium-216) causes recoils which tend to embed the lead in the open porosity porous medium as well as in any other solid exposed to the radon. Because of the rapid diffusion of the radon and the large fraction of the gas phase of the generator being within the pores of the open porosity porous medium a majority of the ^{212}Pb is deposited on and within this medium. Of course, the ^{212}Pb thus deposited undergoes normal radioactive decay so that the amount thus made available in the open porosity porous medium first increases rapidly but then tends to an equilibrium value, after operation for several half lifes of ^{212}Pb.

It should be noted that the amount of ^{212}Pb (and of the other isotopes involved) are extremely minute. Thus 1 mCi of ^{212}Pb corresponds to approximately $2x10^{12}$ atoms of this element which is $3.3x10^{-12}$ moles. Hence the handling and reacting of this lead requires special precautions and procedures which are, however, known in the art. Thus the open porosity porous medium can be dissolved in the presence of mild complexing agents and of traces of "cold" (i.e. non-radioactive) lead, prior to the conjugation reaction with the desired antibody. It may then be removed by dialysis or ultrafiltration and the retentate sterilized and used. On the other hand, if the open porosity porous medium is formed by lyophilized fine latex solids, these may be redispersed in water, conjugated with the antibody and injected, with the ^{212}Pb embedded in them.

As used in the practice of the present invention, the ^{228}Th is in a physical form that does not create a major barrier to the diffusion of the ^{220}Rn gas formed as the ^{228}Th decays, and preferably is amorphous or microcrystalline. As the quantity of ^{228}Th required is extremely small, it will normally be diluted with a carrier for ease of handling and to dilute radiation damage produced by its decay. Alkaline-earth compounds, particularly barium salts are a preferred diluent because of their chemical similarity to thorium. Among such salts, those of the higher aliphatic acids, particularly stearate and palmitate are preferred as these are known to readily release the radon as it is produced (they have high "emanating power") as described by A.C. Wahl and W.R. Daniels, J. Inorg. Nucl. 6:278-287 (1958), which is incorporated herein by reference.

Alternatively, ^{228}Th compounds can be ground into super fine particles which are dispersed in a matrix selected from the group consisting of similarly powdered graphite, alumina, and inert ceramic.

As used herein, the term "gas permeable barrier" refers to a chemical or physical barrier which would serve to constrain the immobilized parent isotope but which is permeable to the gas phase intermediary. Examples of such barriers include layers of open-porosity solids such as stainless steel (or other metal) screens or sintered powder, ceramic porous discs, porous plastics, microporous membranes.

As used herein, "recovering" as it refers to the desired daughter isotopes means obtaining the daughter

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isotopes either with or from the open porosity porous medium. For example, where the open porosity porous medium is water soluble, the open porosity porous medium can be dissolved in water in order to obtain a solution whose principal radioactivity results from the daughter isotopes. Alternatively, where the open porosity porous medium is lyophilized microspheres or antibody, the material can be removed and utilized directly. Thus while in some cases the isotopes are extracted or otherwise removed from the open porosity porous medium, it is also intended that the porous medium, it is also intended that the medium itself, or a derivative, can be used without separating the isotopes therefrom.

As used herein, the term "open porosity porous medium" refers to a solid of substantial bulkiness so that when placed in the receiving compartment the pores within this solid form an important part of the gas phase within the generator and especially of that within the receiving chamber. This porosity is "open" in the sense that it is interconnected so that the gaseous intermediaries can readily diffuse into it, preferably into most of it. Many powders when simply poured into the receiving chamber satisfy these requirements, as do many lyophilized materials. The solid itself has sufficient density such that substantially all of the recoiling daughter will be captured by the open porosity porous medium prior to reaching the side of the container defining the closed chamber. Examples of such open porosity porous media include powdered urea, glucose or other sugars, or inorganic salts; lyophilized antibodies or microspheres. In addition, the open porosity medium must satisfy chemical and biological requirements depending on the use of the daughter isotope, such as being soluble or dispersible in water, being separable from the antibody conjugate, being free of objectionable impurities, particularly other heavy metals, and the like. Such requirements will vary with the particular utilization desired.

Among solids which form suitable open porosity porous media are urea, particularly the ultra-pure grade obtainable from ICN Biochemicals, of Irvine, California, glucose, and sodium chloride, as well as lyophilized materials such as proteins, antibodies, latexes and other particles.

Microspheres as used in this invention are spheres of less than 10 μm in diameter and more than about 0.02 μm, generally made from polymers such as polystyrene, polymethyl-methacrylate, available commercially as aqueous dispersions. Lyophilization is a process by which solvent, such as water, is removed from a frozen solution or dispersion by sublimation of the solvent. In order to facilitate the redispersal of the solute, a wetting agent such as Triton 100 can be added.

Although the invention can be used to generate various isotopes as long as they decay through a gas phase intermediary, the invention will be described with particular reference to producing ^{212}Pb from ^{228}Th. Generating ^{212}Pb from ^{228}Th as taught by the present invention provides a quick, on-site generation and isolation of a high purity product. The process and generator of the present invention produces ^{212}Pb simply, efficiently, and economically in a most desirable form that can be used in any desired application.

The complete sequence of the spontaneous radioactive decay of ^{228}Th is shown in Table I. For the purpose of this invention this can be simplified to the following scheme

$$^{228}\text{Th} \xrightarrow[1.9\text{Y}]{} {}^{220}\text{Ra} \xrightarrow[1\text{min}]{} {}^{212}\text{Pb} \xrightarrow[10\text{hr}]{} {}^{212}\text{Bi} \xrightarrow[1\text{ hr}]{} {}^{208}\text{Pb}\ \text{stable}$$

indicating the main isotopes and their approximate half lives. During each indicated decay alpha, gamma, and in some cases, beta radiations are produced (except in the decay of ^{212}Pb which produces only betas and gammas).

The therapeutic potential of ^{212}Pb (or its daughter ^{212}Bi) is due mainly to its providing alpha particles of about 6 and 9 MV energy which correspond to some 40 and 90 μm penetration in tissue i.e., killing some 4 to 8 cells. This characteristic permits reaching not only the cancer cells corresponding to the antibody used but also other cells which do not respond but are in close vicinity. On the other hand, healthy cells, not in the immediate vicinity of the target ones, are not affected by these alpha particles. While the 10.6 hour half life of ^{212}Pb before decaying is perhaps on the short side of ideal for uses such as cancer therapy, it is a very acceptable length of time to allow for production and purification of the therapeutic complex, administration of the complex to the patient, and time of exposure to the cancer cells.

Thorium-228 has a half life of almost two years and is available commercially which makes it highly desirable as a parent isotope. The raw material for charging the parental chamber of the generator of this invention is thus readily obtained and once charged, the generator could be used for a year or more with only gradual loss of productivity.

Radon-220 being a rare gas will, if allowed, rapidly diffuse away from the thorium and other solids of the parental chamber. With a half-life of only about a minute, it decays to give the desired ^{212}Pb. In order to

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utilize the radon efficiently it is desirable that as much of its decay as practicable occur within the open porosity porous medium. This is facilitated in two ways according to the preferred embodiment of this invention.

1) The thorium is in a matrix having high emanating power. The distance between the parent source and the receiving open porosity medium is made short. The porous membrane separating the two chambers has a large area, high porosity and slight thickness.

2) The volume of the parental chamber is made as small as practicable compared to that of the pores of the open porosity porous medium. A stable gas will distribute itself proportionately to the available gas-phase volumes.

As radon is being generated and is decaying, its concentration is decreasing from the source to the distal end of the open porosity medium, and diffusion continuously proceeds in this direction. Experiments showed that little is gained by making the receiving chamber much longer than about 1 cm as most of the radon would decay before diffusing much longer distances. By using a shorter column of the open porosity medium one can obtain a smaller amount but a higher concentration of the daughter isotope and vice versa.

TABLE I

Isotope	Half Life	Radiation	Energy (Mev)
^{228}Th	1.9 Years	Alpha	8.41
^{224}Ra	3.6 Days	Alpha	5.68
^{220}Rn	54.5 Seconds	Alpha	6.28
^{216}Po	0.15 Second	Alpha	6.77
^{212}Pb	10.6 Hours	Beta	0.35
^{212}Bi	60.5 Minutes	Beta Alpha	2.24 6.05
^{212}Po	$3x10^{-7}$ Sec.	Alpha	8.78
^{208}Tl	3.1 Minutes	Beta	1.42
^{208}Pb	(Stable)		

A generator which can be utilized in the practice of this invention is illustrated in the Figures. The generator can be remotely manipulated in a closed shielded chamber or can be handled in a glove box. As shown in Figure 1 and 2, the generator comprises a parental chamber 10, a receiving chamber 12, and a gas elute means such as gas permeable membrane 14 interposed between and separating the two chambers 10 and 12. The gas permeable membrane 14 must have a pore size sufficient to permit the rapid diffusion of the gaseous intermediary therethrough while, at the same time, preventing the parent isotope from passing into receiving chamber 12. For safety purposes, diffusion membrane 14 preferably comprises a porous support member such as a fritted metal disk which can be made from stainless steel. The generator shown in Figure 1 is formed by a threaded tubular housing 20 having one end thereof closed by end cap 22, which is held in place by flanged cap nut 24. The interior portion of tubular housing 20 has an internal flange 26 at one end thereof which encircles the interior cylindrical surface, and against which the diffusion membrane 14 is positioned. Diffusion membrane 14 should be spaced from end cap 22 by a small distance sufficient to form parental chamber 10 between end cap 22 and the diffusion membrane 14. Parental chamber 10 should be small compared to receiving chamber 12 as indicated above. The volume of receiving chamber should be at least 5 times and preferably 20 times larger than the volume of the parental chamber.

Bushing 28 is threaded into the other end of tubular housing 20 such that its circular inner edge holds

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diffusion membrane 14 against flange 26, thereby defining one end of a smooth interior cylindrical chamber. An elongated end cap 30 is slidably inserted into the cylindrical chamber within bushing 28 so as to form collection chamber 12 between diffusion member 14 and the inner end of end cap 30. Flanged nut cap 32 is threaded onto bushing 28 to hold end cap 30 in place. For safety reasons, all of the structural components of generator 8 are preferably fabricated of a material that will not absorb the ^{220}Rn gas or be decomposed by radiation, and has a melting point in excess of 1,000° C for fire safety. A particularly preferred material is 316 stainless steel.

In accordance with the preferred practice of this invention, the starting material, i.e., ^{228}Th, is used in a physical form that does not create a barrier to the diffusion of the ^{220}Rn gas formed as the ^{228}Th decays. For example, ^{228}Th can be obtained commercially in the form of thorium-228 nitrate (from Isotope Products Laboratories in Burbank, California). Wahl and Daniels, Supra, teach the coprecipitation of ^{228}Th and barium stearates. Their procedure involves heating aqueous solutions of sodium stearate to "60-75" degrees centigrade. This causes problems with vapor condensation in a usual, unventilated, glove box. Any ventilation must insure the decay of ^{220}Rn which is continuously produced and is not adsorbed by conventional filters. Therefore, according to this invention, spiked barium stearate is produced by a metathetical reaction in solution between barium nitrate and a stearate which is soluble at room temperature such as tetramethyl ammonium stearate. The latter is in turn produced by reaction of tetramethyl ammonium hydroxide with stearic acid. Tetra ethyl ammonium hydroxide or the tetra butyl or tetra isopropyl compounds may also be used.

The tetramethyl ammonium stearate solution is prepared outside the glove box by heating an excess of stearic acid with a tetraethyl ammonium hydroxide solution and adding the latter until phenolphthalein indicator turns pink. In the glove box, the ^{228}Th solution is added to a barium nitrate solution and the excess nitric acid (accompanying the thorium) is neutralized with tetraethyl ammonium hydroxide. Then, with good stirring, the stearate solution is added gradually to the barium spiked solution. The precipitate flocculates near the equivalence point and near neutrality. It is then filtered, sucked dry and placed with the filter in the parental chamber of the generator and dried over silica gel. The parental chamber is then closed.

If the receiving chamber is also closed, i.e., both plungers 22 and 30 are inserted and secured with end caps 24 and 32, the escape of radon from the generator is prevented and it can be removed from the glove box and stored in any appropriately shielded space or transported to another laboratory or hospital.

The generator is ready to produce the daughter isotopes whenever the receiving chamber is loaded with the open porosity medium and closed. This can be done in a chemical hood or a more sophisticated containment as the amount of radon escaping in the short time required, is minimal. Once closed, the generator can be stored in s shielded place. After a time necessary for the desired amount of ^{212}Pb to accumulate, the reactor is taken back into the hood, the receiving comportment opened and the open porosity porous medium removed and a material containing the daughter isotope recovered, such as by pouring the open porosity porous medium into an aqueous solution of a mild complexing agent for lead. The receiving chamber is then reloaded if desired and closed. After a short time, sufficient for the radon released upon opening the receiving chamber (and that contained in the open porosity medium) to decay adequately, the solution can be removed from the hood and used for the preparation and administration of a therapeutic product.

Alternatively, the ^{228}Th used in the present invention can be a physical mixture in which a ^{228}Th salt has been ground into extremely fine particles to destroy its macroscopic crystal structure, and the super fine particles of ^{228}Th are dispersed within a porous matrix, such as, for example, similarly powdered graphite, that will not absorb the ^{220}Rn gas. The mixture can be compacted so that the ^{228}Th is encapsulated within the graphite and forms a graphite disc 40 as shown in Figure 2. This embodiment gives the ^{228}Th sufficient bulk for handling purposes while allowing for the even diffusion of radon gas while preventing the formation of thorium crystals. Other inert materials which allow free diffusion of the ^{220}Rn gas therethrough and are not subject to important decomposition by radiation may be used to form such a porous matrix for the ^{228}Th, including but not limited to alumina and inert ceramic.

An alternate embodiment for the reactor of the present invention is shown in Figure 2. The reactor 100 essentially comprises cylindrical body 110 whose cross section is in the form of a cross which is wider at the upper portion thereof. The body is externally threaded on the upper and lower portions. The gas permeable membrane 14 rests against the lip formed where the cylindrical chamber in body 110 increases in diameter, thereby separating the cylindrical chamber into a parental chamber 10 and a receiving chamber 12. To obtain the desired spacing for parental chamber 10, a seal ring 120 of appropriate thickness may be placed on top of diffusion membrane 14. A seal 130 is then slidably inserted into the upper portion of the body, where it is held in place against seal ring 120 by seal cap 140 which is threaded onto the upper portion of the body. An elongated plunger 150 is slidably inserted into the aperture in the bottom portion of

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the plunger body 110 so as to provide collection chamber 12 between the diffusion membrane 14 and the inner end of plunger 150. Plunger 150 is held in place by plunger cap 160 which is threaded onto the lower portion of plunger body 110. As before, all of the structural components of reactor 100 are preferably made from 316 stainless steel. However, since seal ring 120 must be compressible in addition to having a high melting point, it is preferred that it be made from materials such as gold, copper or nickel.

While the above described process is specific to the use of the generator as illustrated, and describes the best mode known for the practice of the invention, it should be apparent that other procedures could be utilized and other reactor embodiments fashioned to produce the lead isotope, relying on the same or comparable principles to effect the objects of this invention. For example, while the above described reactor utilizes a diffusion membrane to separate the two adjacent chambers, it is apparent that the reactor could be designed such that the two chambers are physically separated from each other and connected by a passageway through which the gaseous product could diffuse without permitting transfer of any solid material, e.g., a stopcock. Thus, when the stopcock is opened, the gaseous ^{220}Rn diffuses from parental chamber $\overline{10}$ into the collection chamber 12. It is apparent that other such modifications could be made to the process and reactor without departing from the spirit of the invention.

Although the invention has been described with reference to the presently preferred embodiment, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

Claims

1. A method for obtaining daughter isotopes produced from parent isotopes by a chain of spontaneous decay which includes a normally gaseous intermediary isotope, comprising the steps of:
   (a) providing said parent isotope in gas phase contact with a gas permeable barrier impervious to said parent isotope;
   (b) permitting said gaseous intermediary isotope to diffuse through said gas permeable barrier into a chamber containing an open porosity porous medium;
   (c) maintaining said gaseous intermediate in said medium for a time sufficient for at least a portion of said gaseous intermediate to decay to said daughter isotopes are captured by said open porosity porous medium; and
   (d) recovering said daughter isotopes from said receiving chamber.

2. The method of claim 1, wherein said parent isotope is maintained in a first closed chamber.

3. The method of claim 1, wherein said recovery step comprises dispersing said medium in water.

4. The method of claim 1, wherein said recovery step comprises dissolving said medium in water.

5. The method of claim 1, wherein said open porosity porous medium is urea.

6. The method of claim 1, wherein said open porosity porous medium is glucose.

7. The method of claim 1, wherein said open porosity porous medium is an inorganic salt.

8. The method of claim 1, wherein said open porosity porous medium is lyophilized antibody.

9. The method of claim 1, wherein said lyophilized antibody is conjugated to a chelating agent.

10. The method of claim 1, wherein said open porosity porous medium is lyophilized microspheres.

11. The method of claim 1, wherein said immobilized parent isotope is in the form of a long hydrocarbon carboxylic acid salt.

12. The method of claim 11, wherein the long hydrocarbon carboxylic acid salt is prepared by a metathetical reaction from a second salt of said long hydrocarbon carboxylic acid which is freely soluble in water at room temperature.

13. The method of claim 12, wherein said second salt is selected from the group consisting of tetramethyl,

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tetraethyl, tetrabutyl and tetraisopropyl compounds.

14. A method for obtaining ^{212}Pb, comprising the steps of:
(a) providing ^{228}Th in gas phase contact with a gas permeable barrier impervious to ^{228}Th;
(b) permitting gaseous ^{220}Rn formed by the decay of ^{228}Th to diffuse through the gas permeable barrier into a receiving chamber containing an open porosity porous medium;
(c) maintaining said gaseous ^{220}Rn in said receiving chamber for a time sufficient to permit at least a portion of the ^{220}Rn to decay to ^{212}Pb a portion of which ^{212}Pb recoils into and is captured by the open porosity porous medium; and
(d) recovering the ^{212}Pb from said receiving chamber.

15. The method of claim 14, wherein said parent isotope is in the form of a long hydrocarbon carboxylic acid salt.

16. The method of claim 14, wherein said long hydrocarbon carboxylic acid is selected from the group consisting of stearic acid, palmitic acid, sebacic acid, caproic acid, lauric acid and myristic acid.

17. The method of claim 14, wherein said immobilized parent isotope is dispersed in a matrix of super fine particles comprising charcoal, graphite inert ceramics and alumina.

18. The method of claim 14, wherein said permeable barrier is a membrane.

19. The method of claim 14, wherein said open porosity porous medium is urea.

20. The method of claim 14, wherein said open porosity porous medium is glucose.

21. The method of claim 14, wherein said open porosity porous medium is a chloride.

22. The method of claim 14, wherein said open porosity porous medium is lyophilized antibody.

23. The method of claim 14, wherein said lyophilized antibody is conjugated to a chelating agent.

24. A generator for preparing radioisotopes produced from the decay of a parent isotope via a rare gas intermediary comprising:
a parental chamber for immobilizing the parent isotope as it decays to the gaseous intermediary;
a receiving chamber adjacent said parental chamber containing an open porosity porous medium;
a diffusion means separating said container and said closed chamber which permits said gaseous intermediary to diffuse from said container into said closed chamber and prevents said parent isotope from entering said closed chamber, wherein as said gaseous intermediary decays the resulting radioactive isotopes recoil into said open porosity porous medium.

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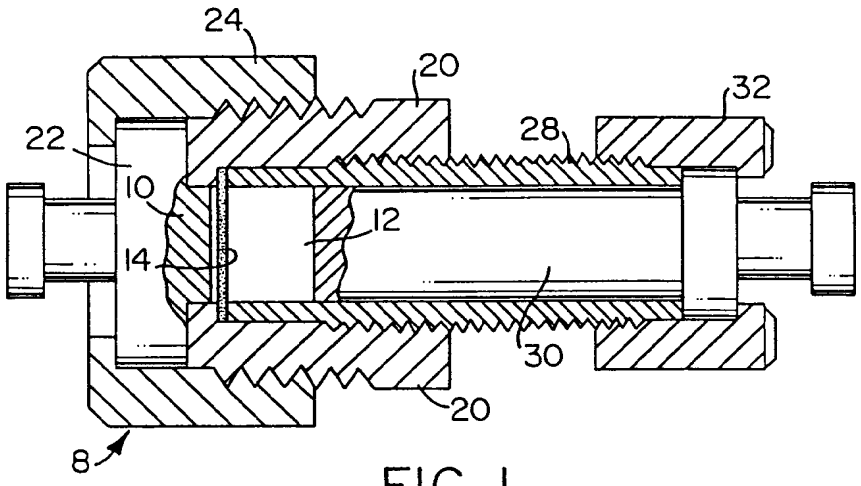
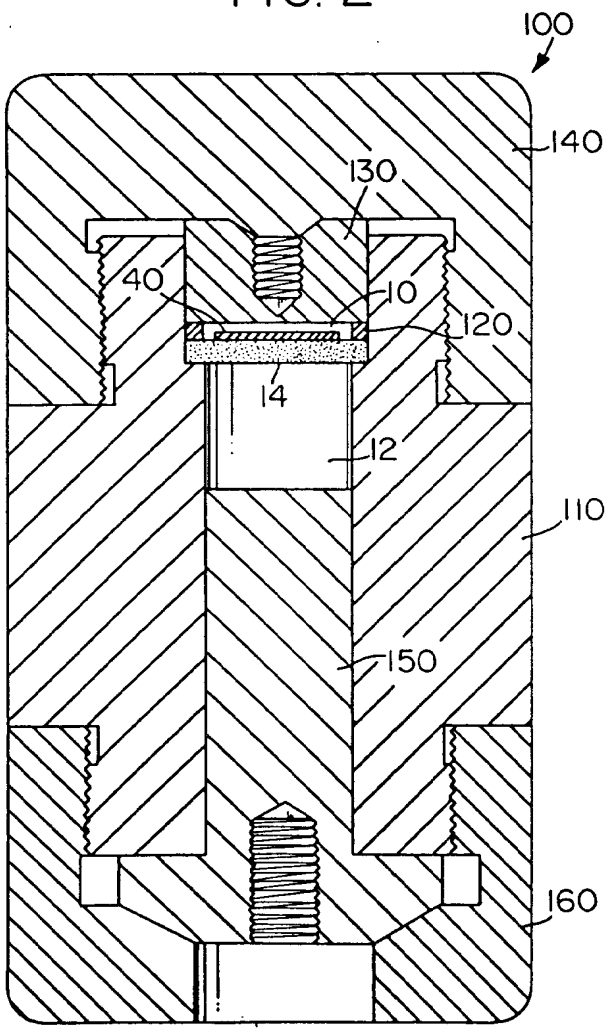

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FIG. 1

FIG. 2


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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 25 0183

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-4 663 129 (ATCHER) * claims 1,2,4,8; example *	1-3,14-23	G 21 G 4/08 A 61 K 43/00
X	INT. J. RAD. APPL. INSTRUM. PART A. vol. 39, no. 4, 1988, EXETER. GB. pages 283 - 286; ATCHER ET AL.: 'An improved Generator for the Production of 212-Pb and 212-Bi from 224-Ra ' * page 283, right column - page 284, left column *	1-3,14-23	
A	Derwent File Supplier WPIL Derwent Publications London. UK & JP.A 57021313 (Tokyo Health) * abstract *	1,14-24	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)
G 21 G A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	14 October 91	NICOLAS H.J.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

INFORMATION DISCLOSURE STATEMENT

First Inventor: Roy Hartvig Larsen	**Conf. No.:** Unassigned
App. No.: Unassigned	**Filed:** Herewith
Examiner: Unassigned	**Art Unit:** Unassigned
Title: PRODUCTION OF HIGHLY PURIFIED 212PB	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

References and Listing

Pursuant to 37 CFR 1.56, an Information Disclosure Statement listing references is provided herewith. Copies of any listed foreign and non-patent literature references are being submitted.

No Disclaimers

To the extent that anything in the Information Disclosure Statement or the listed references could be construed as a disclaimer of any subject matter supported by the present application, Applicant hereby rescinds and retracts such disclaimer.

Timing of Disclosure

This Information Disclosure Statement is being filed within three months of the filing date or date of national phase entry, with an RCE or before receipt of a First Office Action after an RCE, and no fee is believed to be required.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application No.	Unassigned
	Filing Date	Herewith
	First Named Inventor	Roy Hartvig Larsen
	Art Unit	Unassigned
(Multiple sheets used when necessary)	Examiner	Unassigned
SHEET 1 OF 1	Attorney Docket No.	AERA001.005APC

U.S. PATENT DOCUMENTS					
Examiner Initials	Cite No.	Document Number *Number - Kind Code (if known)* Example: 1,234,567 B1	Publication Date MM-DD-YYYY	Name	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
	1	2015/0170776 A1	06-18-2015	TORGUE, Julien et al.	
	2	2018/0047474 A1	02-15-2018	O'HARA, Matthew J.	

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	3	EP 0466290 A1	01-15-1992	Brunswick Corporation		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	**T[1]**
	4	International Search Report for PCT/EP2020/084701 dated February 17, 2021	

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Examiner Signature	Date Considered

***Examiner:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

AdvanCell

T[1] - Place a check mark in this area when an English language Translation is attached.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
P2601WO00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2020/084701	4 December 2020 (04-12-2020)	5 December 2019 (05-12-2019)
Applicant		
SCIENCONS AS		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/084701

A. CLASSIFICATION OF SUBJECT MATTER
INV. G21G1/00 A61K51/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G21G A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 466 290 A1 (BRUNSWICK CORP [US]) 15 January 1992 (1992-01-15)	1-35,37
A	page 2, line 45 - page 3, line 2; claims; figures	36,38

X	US 2018/047474 A1 (OHARA MATTHEW J [US]) 15 February 2018 (2018-02-15)	1-35,37
A	paragraph [0012] - paragraph [0029]; claims; figures	36,38

A	US 2015/170776 A1 (TORGUE JULIEN [US] ET AL) 18 June 2015 (2015-06-18) abstract; figures	1-38

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2021	17/02/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Smith, Christopher

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/084701

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0466290 A1	15-01-1992	CA 2046546 A1	11-01-1992
		EP 0466290 A1	15-01-1992
		JP H05264794 A	12-10-1993
		US 5038046 A	06-08-1991
US 2018047474 A1	15-02-2018	NONE	
US 2015170776 A1	18-06-2015	AU 2013265268 A1	18-12-2014
		DK 2854870 T3	06-08-2018
		EP 2854870 A1	08-04-2015
		ES 2683398 T3	26-09-2018
		FR 2990956 A1	29-11-2013
		JP 6392210 B2	19-09-2018
		JP 2015523555 A	13-08-2015
		PL 2854870 T3	31-01-2019
		PT 2854870 T	03-10-2018
		SI 2854870 T1	30-10-2018
		TR 201811310 T4	27-08-2018
		US 2015170776 A1	18-06-2015
		US 2018308600 A1	25-10-2018
		WO 2013174949 A1	28-11-2013

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	06/02/2022 05:31:16 PM ET	AERA001.005APC

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Evelyn Salcido
PATENT CENTER #	60699221	AUTHORIZED BY	Eric Furman
CUSTOMER #	20995	FILING DATE	-
INTL. APPLICATION #	PCT/EP2020/084701	INTL. FILING DATE	12/04/2020
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Roy H. Larsen

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 2564	E202262H32261380	Evelyn Salcido

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2617	SEARCH FEE, EXAMINATION FEE OR OATH OR DECLARATION AFTER THE DATE OF COMMENCEMENT OF THE NATIONAL STAGE	80.00	1	80.00
2631	BASIC NATIONAL STAGE FEE	160.00	1	160.00
2633	NATIONAL STAGE EXAMINATION FEE - ALL OTHER SITUATIONS	400.00	1	400.00
2615	EACH CLAIM IN EXCESS OF 20	50.00	18	900.00
2642	NATIONAL STAGE SEARCH FEE -	270.00	1	270.00

SEARCH REPORT PREPARED AND
PROVIDED TO USPTO

TOTAL AMOUNT:	**$1,810.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2020/084701	04.12.2020	05.12.2019

International Patent Classification (IPC) or both national classification and IPC
INV. G21G1/00 A61K51/12

Applicant
SCIENCONS AS

1. 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 under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Smith, Christopher Telephone No. +49 89 2399-0

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-11, 19, 23, 26-28, 30-38
	No:	Claims	1-7, 12-18, 20-22, 24, 25, 29
Inventive step (IS)	Yes:	Claims	36, 38
	No:	Claims	1-35, 37
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Item V

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

Reference is made to the following documents:

D1 EP 0 466 290 A1 (BRUNSWICK CORP [US]) 15 January 1992 (1992-01-15)

D2 US 2018/047474 A1 (OHARA MATTHEW J [US]) 15 February 2018 (2018-02-15)

1 The present application does not meet the criteria of **Article 33(2) PCT**, because the subject-matter of **claim 1** is not novel:

1.1 D1 discloses (see in particular the figures and their description): a method (D1: claim 14) for obtaining a container (12) comprising ^{212}Pb (claim 14) on the walls comprising the steps of: providing an assembly (Fig. 14) comprising a first part (28) and a second part (20), wherein the first part comprises a container (12) and the second part comprises a ^{212}Pb precursor isotope source (claim 14), connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container (membrane 14 assures this) and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn,^{216}Po and/or ^{212}Pb (implicit of ^{228}Th decay), and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

The subject-matter of **claim 1** is not considered novel, **Article 33(2) PCT**.

1.2 D2 also clearly discloses all features of **claim 1**, see for instance claims 13 - 20, as well as the figures (assembly 100, parent 4, container 24), **Article 33(2) PCT**.

1.3 Similar reasoning applies to the subject-matter of the corresponding independent apparatus **claims 2** and **3**, which therefore is also considered not novel, **Article 33(2) PCT**, with respect to D2.

2 Dependent **claims 4 - 35, 37** do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty or inventive step: these claims either refer to implicit or obvious features and minor adjustments which fall within the scope of work performed by a person skilled in the art working with the apparatus known from D1 or D2, or to values (volumes, activities) which appear to be arbitrarily chosen without any corresponding technical effect, see also Item VIII below.

3 The combination of the features of dependent **claims 36** and **38** is neither known from, nor rendered obvious by, the available prior art. None of the prior art documents found hint or suggest the use of a glass flask placed up-side down on its cap containing the precursor, which the applicant has found to be a convenient way of reducing the contamination of the produced isotope.

The subject-matter of these claims is considered to be novel and involve an inventive step, **Articles 33(2),(3) PCT.**

Item VIII

Certain observations in the international application

4 Dependent **claims 4 - 36** contain both apparatus and method features. The aforementioned claims therefore lack clarity and as such do not meet the requirements of **Article 6 PCT**.

The features of the claims are not provided with reference signs placed in parentheses, **Rule 6.2(b) PCT**.

Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in documents D1 and D2 is not mentioned in the description, nor is this document identified therein.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AERA001.005APC
	Application Number	
Title of Invention	PRODUCTION OF HIGHLY PURIFIED 212PB	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Roy	H.	Larsen	

Residence Information (Select One) US Residency ● Non US Residency Active US Military Service

City	Oslo	Country of Residence i	NO

Mailing Address of Inventor:

Address 1	Sørbråtveien 12		
Address 2			
City	Oslo	**State/Province**	
Postal Code	0891	**Country** i	NO

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	20995		
Email Address	efiling@knobbe.com	Add Email	Remove Email

Application Information:

Title of the Invention	PRODUCTION OF HIGHLY PURIFIED 212PB		
Attorney Docket Number	AERA001.005APC	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AERA001.005APC
	Application Number	
Title of Invention	PRODUCTION OF HIGHLY PURIFIED 212PB	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	20995		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
Present	a 371 of international	PCT/EP2020/084701	2020-12-04

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AERA001.005APC
	Application Number	
Title of Invention	PRODUCTION OF HIGHLY PURIFIED 212PB	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
19213759.4	EP	2019-12-05	

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
20172038.0	EP	2020-04-29	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AERA001.005APC
	Application Number	
Title of Invention	PRODUCTION OF HIGHLY PURIFIED 212PB	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AERA001.005APC
	Application Number	
Title of Invention	PRODUCTION OF HIGHLY PURIFIED 212PB	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Sciencons AS		
Mailing Address Information For Applicant:			
Address 1	Gullhaugveien 7		
Address 2			
City	Oslo	**State/Province**	
Country	NO	Postal Code	NO-0484
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AERA001.005APC
	Application Number	
Title of Invention	PRODUCTION OF HIGHLY PURIFIED 212PB	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Eric Furman/			Date (YYYY-MM-DD)	2022-06-02
First Name	Eric	Last Name	Furman	Registration Number	45664

Additional Signature may be generated within this form by selecting the Add button. Add

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AERA001.005APC
	Application Number	
Title of Invention	PRODUCTION OF HIGHLY PURIFIED 212PB	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/084701

A. CLASSIFICATION OF SUBJECT MATTER
INV. G21G1/00 A61K51/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G21G A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 466 290 A1 (BRUNSWICK CORP [US]) 15 January 1992 (1992-01-15)	1-35,37
A	page 2, line 45 - page 3, line 2; claims; figures	36,38

X	US 2018/047474 A1 (OHARA MATTHEW J [US]) 15 February 2018 (2018-02-15)	1-35,37
A	paragraph [0012] - paragraph [0029]; claims; figures	36,38

A	US 2015/170776 A1 (TORGUE JULIEN [US] ET AL) 18 June 2015 (2015-06-18) abstract; figures	1-38

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2021	17/02/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Smith, Christopher

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/084701

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0466290 A1	15-01-1992	CA 2046546 A1	11-01-1992
		EP 0466290 A1	15-01-1992
		JP H05264794 A	12-10-1993
		US 5038046 A	06-08-1991
US 2018047474 A1	15-02-2018	NONE	
US 2015170776 A1	18-06-2015	AU 2013265268 A1	18-12-2014
		DK 2854870 T3	06-08-2018
		EP 2854870 A1	08-04-2015
		ES 2683398 T3	26-09-2018
		FR 2990956 A1	29-11-2013
		JP 6392210 B2	19-09-2018
		JP 2015523555 A	13-08-2015
		PL 2854870 T3	31-01-2019
		PT 2854870 T	03-10-2018
		SI 2854870 T1	30-10-2018
		TR 201811310 T4	27-08-2018
		US 2015170776 A1	18-06-2015
		US 2018308600 A1	25-10-2018
		WO 2013174949 A1	28-11-2013

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION, OBTENTION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

AERA A/S
Gammel Kongevej 60, 18th floor
1850 Frederiksberg C
DANEMARK

Date of mailing *(day/month/year)* 21 December 2020 (21.12.2020)	
Applicant's or agent's file reference P2601WO00	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2020/084701	International filing date *(day/month/year)* 04 December 2020 (04.12.2020)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 05 December 2019 (05.12.2019)
Applicant SCIENCONS AS	

The applicant is hereby notified of the date of receipt (or of obtaining by the International Bureau) of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to the date of receipt, **the priority document concerned was submitted or transmitted to or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-*bis*)**. This Form replaces any previously issued notification concerning submission, transmittal or obtaining of priority documents.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
05 December 2019 (05.12.2019)	19213759.4	EP	09 December 2020 (09.12.2020)
29 April 2020 (29.04.2020)	20172038.0	EP	09 December 2020 (09.12.2020)

The letters "NR" denote a priority document which, on the date of mailing of this Form, had not yet been received or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-*bis*). Where the applicant has failed to either submit, request to prepare and transmit, or to request the International Bureau to obtain the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

An asterisk "*" next to a date of receipt, denotes a priority document submitted or transmitted to or obtained by the International Bureau but not in compliance with Rule 17.1(a), (b) or (b-*bis*) (the priority document was received after the time limit prescribed in Rule 17.1(a); the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b) or the request to the International Bureau to obtain the priority document was made after the applicable time limit under Rule 17.1(b-*bis*)). Even though the priority document was not furnished in compliance with Rule 17.1(a), (b) or (b-*bis*), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
Nora Lindner
e-mail pct.team5@wipo.int
Telephone No. +41 22 338 74 05

AdvanCell
1/L7LH23AG9YPJG0
Ex. 1006 - Page 47

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

AERA A/S
Gammel Kongevej 60, 18th floor
1850 Frederiksberg C
Danemark

Date of mailing *(day/month/year)*
12 March 2021 (12.03.2021)

Applicant's or agent's file reference
P2601WO00

IMPORTANT NOTIFICATION

International application No.
PCT/EP2020/084701

International filing date *(day/month/year)*
04 December 2020 (04.12.2020)

1. The following indications appeared on record concerning:

☐ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
LARSEN, Roy, H.
Lunden 20
0598 Oslo
Norway

State of Nationality | State of Residence
Telephone No.
Facsimile No.
E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
LARSEN, Roy, H.
Sørbråtveien 12
0891 Oslo
Norway

State of Nationality | State of Residence
Telephone No.
Facsimile No.
E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
Campin Helene
e-mail pct.team5@wipo.int
Telephone No. +41 22 338 74 05

AdvanCell
Ex. 1006 - Page 48
1/GCVK7HQFYCMMG0

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH DO NOT APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

AERA A/S
Niels Hemmingsens Gade 10, 5th floor
1153 Copenhagen K
DANEMARK

Date of mailing *(day/month/year)* 08 July 2021 (08.07.2021)		
Applicant's or agent's file reference P2601WO00		**IMPORTANT NOTICE**
International application No. PCT/EP2020/084701	International filing date *(day/month/year)* 04 December 2020 (04.12.2020)	Priority date *(day/month/year)* 05 December 2019 (05.12.2019)
Applicant SCIENCONS AS		

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply,** please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
10 June 2021 (10.06.2021)

   None

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

   LU, TZ

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

   For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of **19 months** from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **20 MONTHS** from the priority date.

   In practice, **time limits other than the 20-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For **regular updates on the applicable time limits** (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/guide/index.html.

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
Nora Lindner
e-mail pct.team5@wipo.int
Telephone No. +41 22 338 74 05

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

AERA A/S
Niels Hemmingsens Gade 10, 5th floor
1153 Copenhagen K
DANEMARK

Date of mailing *(day/month/year)* 07 April 2022 (07.04.2022)	
Applicant's or agent's file reference P2601WO00	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2020/084701	04 December 2020 (04.12.2020)	05 December 2019 (05.12.2019)

Applicant

SCIENCONS AS

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
10 June 2021 (10.06.2021)

   CN, EP, KP, KR, MK, MZ, NA, NG, PG, TM

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

   AE, AG, AL, AM, AO, AP, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KW, KZ, LA, LC, LK, LR, LS, LY, MA, MD, ME, MG, MN, MW, MX, MY, NI, NO, NZ, OA, OM, PA, PE, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TN, TR, TT, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

   For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/guide/index.html.

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
Nora Lindner
e-mail pct.team5@wipo.int
Telephone No. +41 22 338 74 05

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**06/02/2022 05:31:16 PM ET**	**AERA001.005APC**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Evelyn Salcido
PATENT CENTER #	60699221	FILING DATE	-
CUSTOMER #	20995	FIRST NAMED INVENTOR	Roy H. Larsen
INTL. APPLICATION #	PCT/EP2020/084701	INTL. FILING DATE	12/04/2020
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Eric Furman

Documents

TOTAL DOCUMENTS: 17

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Transmittal.pdf		4	Transmittal of New Application	309 KB
ADS.pdf		8	Application Data Sheet	2174 KB
PCT-EP2020-084701.pdf		39	-	4217 KB
PCT-EP2020-084701-ABST.pdf	(1-2)	2	Abstract	56 KB
PCT-EP2020-084701-SPEC.pdf	(3-27)	25	Specification	1316 KB
PCT-EP2020-084701-	(28-32)	5	Claims	172 KB

CLM.pdf				
PCT-EP2020-084701-DRW.pdf	(33-37)	5	Drawings-only black and white line drawings	2613 KB
PCT-EP2020-084701-371P.pdf	(38-39)	2	Documents submitted with 371 (National Stage) Applications	62 KB
PrelimAmend.pdf		8	-	96 KB
PrelimAmend-A.PE.pdf	(1-1)	1	Preliminary Amendment	78 KB
PrelimAmend-SPEC.pdf	(2-2)	1	Specification	78 KB
PrelimAmend-CLM.pdf	(3-7)	5	Claims	89 KB
PrelimAmend-REM.pdf	(8-8)	1	Applicant Arguments/Remarks Made in an Amendment	78 KB
IBs.pdf		4	Documents submitted with 371 (National Stage) Applications	225 KB
WO.pdf		5	Documents submitted with 371 (National Stage) Applications	178 KB
IDS.pdf		2	-	158 KB
IDS-TRAN.LET.pdf	(1-1)	1	Transmittal Letter	76 KB
IDS-IDS.pdf	(2-2)	1	Information Disclosure Statement (IDS) Form (SB08)	125 KB
EP0466290A1.pdf		10	Foreign Reference	111 KB
ISR.pdf		4	Non Patent Literature	113 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Transmittal.pdf	C42C31DC53FDC0E60DE9187F92C8E66D976A97352CF6A5001 2BC3F399E6AB475EE08A117CBE13EACC8CF813D379A45D4A 4910DB3F527F9A52C6027F40579F4D9
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PCT-EP2020-084701.pdf	5A086965714656CA13C77B0D4E8DD53CC230250F29A8B33912 94AE24392C8B74B7AAC3C704363B0D0F328C83B9836A4469F 5ECBA116D174A6DC5D283F3982DEE
PCT-EP2020-084701-ABST.pdf	1A9765D1969B01ECFDC5F8A53664CE243BA72F0DF1BB7AB1 F84C93A084B7834E21316CAF95E33B1A224DFB7117906A77F8 BE562895356EB572CA13E6C3FFE65C
PCT-EP2020-084701-SPEC.pdf	2C5953E61412507FF4A22B38A0E7A17E733CE9C9160404007E C43075C0DC6870E6F87D2926AE99CCD63DB75A3C1DB5F9FD 11D6B9068F386763BF0410CD20E6BC
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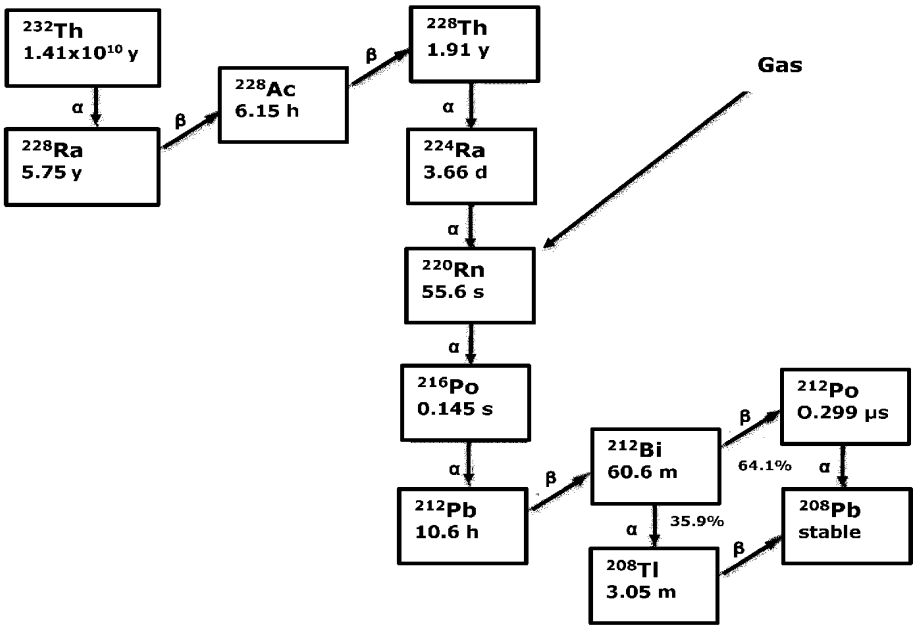
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(57) Abstract: The present invention relates to assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

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Production of highly purified ^{212}Pb

FIELD

The present invention relates to a single chamber diffusion generator (assembly), assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

BACKGROUND

Assemblies for preparing or producing ^{212}Pb have previously been described and based on ^{228}Th bound to stearate in a chamber with another chamber for collecting the ^{212}Pb after ^{220}Rn has diffused from the first chamber (source chamber) to the second chamber (collector chamber).

In another system the $^{228}Th/^{224}Ra$ was extracted from one vessel with a pump generated airflow and $^{220}Rn/^{212}Pb$ collected in another vessel. The system consisted of an “air loop” for transportation of ^{220}Rn and a “fluid loop” for ^{212}Pb rinsing and after rinse collection. This is a quite complex system which is not suitable for shipment and handling, and the potential for leakage or inappropriate use in for example a hospital is significant.

In another system an emanator source is placed inside one chamber and a gas flow passes through and carry ^{220}Rn to another chamber where $^{220}Rn/^{212}Pb$ is collected. After some time, the carrier gas valve is closed, and the collection unit is added a liquid through a top valve and the liquid is collected through a bottom valve. This system is as well relatively complex. Both of these systems need significant work effort of skilled workers and relatively advanced lab equipment and space to operate.

Also, generator systems for ^{212}Pb not relying on ^{220}Rn emanation and diffusion has been presented previously. In one existing generator system ^{224}Ra is bound to ion exchange material and the ^{212}Pb extracted by elution with acid which must be evaporated before it can be used for radiolabeling in another existing system the ^{212}Pb in a solution with ^{224}Ra is used for labelling following the removal of ^{224}Ra by size exclusion purification. Both these methods are working but requires extra time for processing, more so for the first method than the second.

^{212}Pb has a half-life of only 10.6 h. This half-life makes the radioisotope idea for medical applications such as anti-cancer treatment because it acts on its target and without prolonged side effects from a long half-life. However, this feature also makes is difficult to use in a commercial setting involving centralized production and long-distance shipment to end users simply because it decays fast which gives lower yields over time.

Thus a challenge for the current emanation and diffusion systems is transport distances which can reduce efficiency significantly due to decay of ^{220}Rn before reaching the collection vessels. For example, one system reported a total yield from a 3 days operation of 2.01 MBq ^{212}Pb collected compared from a ^{228}Th source of 7.05 MBq, *i.e.* less than 30% yield. Increasing the operation time did not increase the amount collected and the system was sensitive to the air flow rate.

There is a need for alpha-emitter therapeutics for biomedical applications. Lead-212 (^{212}Pb) is a beta-emitter that decays to short lived progenies producing alpha particles and can thus act as an alpha emitter generator *in vivo* useful in alpha emitter therapeutics.

This industry therefore needs an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

SUMMARY

An object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The described system may be termed a single chamber diffusion generator for ^{212}Pb.

In the following, precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb i.e., ^{216}Po, ^{220}Rn, ^{224}Ra etc.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the

second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

In one or more embodiments of the invention the single chamber container assembly is gas tight.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th.The ^{212}Pb activity may vary from typically 0% to 114% of the ^{224}Ra precursor activity in the generator depending on the ingrowth status. The ^{212}Pb activity can be at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % of the ^{224}Ra precursor activity.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the total amount of radioactivity in the single chamber container assembly is 1 kBq – 100 GBq.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose.

In one or more embodiments of the invention a strip or sphere is attached to the second part, which comprises means for holding the strip or sphere, such as a rod.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap.

In one or more embodiments of the invention the second part comprises a rod that is attached to the means for opening and closing the container.

In one or more embodiments of the invention the means for opening and closing the container is a cap, cover or a lid.

In one or more embodiments of the invention the cap, cover or a lid is made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

In one or more embodiments of the invention the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

In one or more embodiments of the invention the substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is less defined as less than 3 % ^{224}Ra of the ^{212}Pb

precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated. The coating may be a film of salt or other suitable material on the inner walls.

In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

DETAILED DESCRIPTION

The present inventors have in response to the need for a simpler, safer system with less size and transport distances to handle the short half-life of ^{220}Rn and ^{212}Pb, designed an assembly whereby the radon producing source is placed inside the collector chamber or container. Instead of using ^{228}Th only as a source is the present invention flexible and can able to use pure ^{224}Ra or a combination of ^{228}Th or ^{224}Ra as source, or even their precursor isotopes (Figure 1).

The assembly of the present inventions can be made very compact and very simple, allowing for a shippable and disposable ^{212}Pb-generator unit. In the present context is assembly, diffusion generator and system are used interchangeably. The described assembly or system may therefore be termed a single chamber diffusion generator for ^{212}Pb.

Thus, an object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the inner walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, and/or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. Examples of such containers or assemblies are described in the examples of the present disclosure and can also be seen in figures 2-5.

An aspect of the invention relates to a method of obtaining a ^{212}Pb solution comprising obtaining the above container comprising ^{212}Pb on the walls and collect the ^{212}Pb in a solution. The ^{212}Pb can be collected in a solution that is in the container before the ^{212}Pb is generated or using a solution that is introduced to the container after the ^{212}Pb has been generated, and then collected. The collection can be done for example using a syringe.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

A huge advantage with the described assembly (or also defined herein as a container, system or a generator) is the ability to supply ^{212}Pb without the activity level is dictated by the short (10.6 h) half-life of ^{212}Pb. With the described system it is possible to produce a diffusion generator in a centralized production facility and ship it to the end user. A portable disposable generator could be made and shipped to *e.g.* a hospital from one end or the world to the other. For such a disposable unit, a pure ^{224}Ra (without ^{228}Th) is preferable as this would become inactive after 40-50 days approximately avoiding generation of long-lived radioactive waste. Such a diffusion source will steadily produce ^{220}Rn/^{212}Pb in a fashion dictated by the half-life of ^{224}Ra (Table 1 and Figure 1). The container, comprising the ^{212}Pb precursor isotope source, will produce ^{212}Pb due to the nature of decaying isotopes. The amount of ^{212}Pb deposited on will depend on several factors including the choice of ^{212}Pb precursor isotope source and time. The time is an important factor. An object of the invention relates to a method for preparing a substantially pure ^{212}Pb solution, the method comprising obtaining the assemblies and containers described herein, wherein the ^{212}Pb precursor isotope source is kept in the sealed assemblies and containers for a given time, the ^{212}Pb precursor isotope source is isolated or removed without coming into contact, and the ^{212}Pb on the walls are then collected by adding a solution that is suitable for collecting the ^{212}Pb. The time that the ^{212}Pb precursor isotope source is kept in the assemblies and containers of the present invention can be from minutes, to hours, to days, to years, depending on the choice of ^{212}Pb precursor isotope source and the amount of ^{212}Pb needed. The time can be at least one day. The time can be at least one day. The time can be at least two days. The time can be at least four

days. The time can be at least a week. The time can be at least two weeks. The time can be at least two weeks. The time can be at least a month. The time can be at least a year.

^{212}Pb is a member of the thorium natural radionuclide series and can be found in materials containing ^{232}Th ($t_{1/2}$=1.4x10^{10} years). The ^{212}Pb precursor can therefore be chosen based on the intended use. A precursor with longer half-life can be chosen to generate an assembly or system that that will act as a ^{212}Pb generator for continuous production over a longer period of time. Alternatively, an isotope with a shorter half-life be used is the intended use for example is at a hospital or similar where generation of long-lived radioactive waste can be problematic. Naturally a mix of different precursors will therefore also be relevant and also where specific assemblies are needed for the generation of a specific amount of ^{212}Pb over a specific period of time.

Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra. Thus, in the following ^{212}Pb precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb, *i.e.* ^{216}Po, ^{220}Rn, ^{224}Ra ^{228}Th, ^{228}Ac, ^{228}Ra, ^{232}Th.

The decay of these radioisotopes can be seen in figure 1 which clearly indicate the possibility of creating a ^{212}Pb precursor isotope source with different decay profiles and different combinations of precursor isotopes will be able to generate ^{212}Pb at different rates over different periods of time.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra. The source can also be each of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra individually, but due to the decay will a mixture naturally over time occur because ^{232}Th will decay to ^{228}Ra and so on. The key is that the gaseous ^{220}Rn is produced because it will diffuse from the source and later settle on the inner walls of the container as ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th. The ^{212}Pb activity may vary from typically 0% to 114% of the ^{224}Ra precursor activity in the generator depending on the ingrowth status. The ^{212}Pb activity can be at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 10 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 10 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 20 % of the ^{224}Ra

precursor activity. The ^{212}Pb activity can be at least at least 30 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 40 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 50 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 60 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 70 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 80 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 90 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 100 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 110 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 20 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 30 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 40 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 50 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 60 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 70 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 80 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 90 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 100 % of the ^{224}Ra precursor activity.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

The assembly working as a ^{212}Pb generator unit can be mass produced in a centralized production facility and shipped to end users for application in production of radiopharmaceuticals. It can also be adapted and used for large scale centralized production of ^{212}Pb. Thus, the amount of radioactivity in the assembly can adjusted according to its intended use. In one or more embodiments of the invention will the total amount of radioactivity in the single chamber container assembly therefore can be 1 kBq – 100 GBq, such as 1 kBq – 10 MBq, such as 100 kBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 kBq – 100 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 kBq – 10 MBq. The total amount of radioactivity in the single chamber container assembly can be 100 kBq – 10 MBq. The total amount of radioactivity in the single chamber container assembly can be 1 MBq – 1 GBq. The total amount of radioactivity in the single chamber container assembly can be 10 MBq – 10 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 MBq – 1 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 GBq – 100 GBq.

In one or more embodiments of the invention will the amount of ^{212}Pb radioactivity in the single chamber container assembly therefore can be 1 kBq – 100 GBq, such as 1 kBq – 10 MBq, such as

100 kBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq. In one or more embodiments of the invention will the amount of ^{212}Pb precursor isotope source radioactivity in the single chamber container assembly therefore can be 1 kBq – 100 GBq, such as 1 kBq – 10 MBq, such as 100 kBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq.

The ^{212}Pb precursor isotope source can be in different forms, sizes and shapes depending on the application type. Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$. The ^{212}Pb precursor isotope source can also be in a dry form or in a liquid solution, such as an aqueous solution or a dispersion. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH. The pH can be 1-14, such as pH 1-6, pH 2-6, pH 2-8, pH 4-8, pH 5-7, pH 6-8, pH 7-8, pH 7,2, pH 8-10, pH 8-12, or pH 10-14.

The solution can be an aqueous solution. The solution can be a 0,1M aqueous HCl solution. This solution can also be used to dissolve the ^{212}Pb on the walls of the assembly.

The assembly working as a generator system may be used for preparing single patient dosing or for multiple patient dosing, or even for industrial use. The amount of radioisotope can therefore be adjusted depending on the application of the assembly.

The ^{212}Pb precursor isotope source can be placed on the rod, either directly or on a strip attached to the rod, typically in a very small liquid volume. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid. Such liquid can be in the amount of 1 µl to 1 ml, such as 1 µl to 10 µl, such as 1 µl to 100 µl.

When the container, which can be a vial, can be empty or contain a small volume of liquid in the bottom, that is not touching the source. In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

It is important that the source does not drip or chip of in a fashion that causes cross contamination of the inner surfaces of the collector unit (container) with source material and that the source and source holder can be removed and or withdrawn from the collector without causing cross contamination by contact.

In one or embodiments the source is surrounded by a grid or encapsulated in a porous material to reduce risk of cross-contamination. This encapsulation can be a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

Thus, in one or more embodiments of the invention the container does or does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion. The container may comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source, and the gas permeable barrier impervious to the ^{212}Pb precursor isotope source can be in contact with the ^{212}Pb precursor isotope source. In one or more embodiments of the invention the single chamber container assembly is gas tight.

Figure 2 shows an example of the single chamber container assembly where the container (the first part) is connected with a cap and a rod attached to the cap is used to hold the ^{212}Pb precursor isotope source (the second part) without having this source touch an inner wall of the container during the entire process.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source can therefore be bound to a non-radioactive material, such as particles or a holding material. These can ensure that the source does not contaminate the container. The ^{212}Pb precursor isotope source can be deposited on a strip, sphere or a rod which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers. The strip or sphere can be attached to the second part or be contained or comprised in the second parts, which comprises means for holding the strip or sphere. Such means can for example be a rod.

In one or more embodiments of the invention the second part comprises, optionally, a rod that is attached to the means for opening and closing the container. The means for opening and closing the container can be a cap, cover or a lid which can be made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose ion exchange resin, natural mineral, polymer. Alternatively, the source is attached to a material placed onto the cap with or without being adhered to the cap. If the cap is placed on the bottom, the source material can be simply placed onto the interior of the cap without touching the ^{212}Pb collector part and kept in place by gravitation. In such case the generator unit should be stored and handled in position whereby cap with the source is always kept at the bottom.

The means for opening and closing the container can comprise the ^{212}Pb precursor isotope source. The ^{212}Pb precursor isotope source can be placed on a sponge, a wool or another substance that is capable of keeping the ^{212}Pb precursor isotope source in the means for opening and closing the container. The wool can be a quartz wool. The wool can also be a mineral wool. The wool can also be a glass wool. The substance that is capable of keeping the ^{212}Pb precursor isotope source in the means for opening and closing the container can be attached by glue, double-sided mounting tape or other means for attachment.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe. The means for holding can be deposited on a strip or sphere which is made of

material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers cellulose ion exchange resin, natural mineral, polymer.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap. An alternative design is where the second part is a rubber cap, or septum of another material permeable, and preferential self-sealing, with a syringe tip, with means for holding the ^{212}Pb precursor isotope source attached to the cap or to the inner walls of the container. In this case will user of the assembly be able to dissolve the ^{212}Pb from the inner walls of the container in an aqueous solution though a syringe that is pushed through the cap. The resulting ^{212}Pb in aqueous solution can afterwards be collected by the same syringe which will generate the option of working in a GMP environment which can be directly applied for patient use. Thus, in one embodiment the ^{212}Pb precursor isotope source be withdrawn into a capsule or similar allowing the container to be washed e.g., by using a solution transferred via a syringe through a rubber septum, without having to disassemble the two units. In another embodiment the assembly can be autoclaved, and the solution be of a physiological acceptable composition containing a chelator for disease targeting allowing withdrawal into a syringe and direct infusion with or without the use of a sterile syringe filter. In one embodiment the assembly including all subunits is autoclavable and with a syringe permeable zone on the cap allowing aseptic extraction of ^{212}Pb from the assembly.

After a few hours or days of operation the assembly with the ^{212}Pb precursor isotope source can be used for producing ^{212}Pb by retracting the ^{212}Pb precursor isotope source, e.g., by changing the cap with the attached ^{212}Pb precursor isotope source to a new cap without radioactivity and washing the inner surface with a suitable solution to dissolve surface deposited ^{212}Pb and progenies. Since the ^{212}Pb solution is free from long lived predecessor radionuclides it can be used directly without further chemical processing to label carrier molecules for e.g. cancer therapy.

The ^{212}Pb precursor isotope source can associated with a needle, rod or a strip of a material of which ^{212}Pb precursor isotope source is attached to allow diffusion of ^{220}Rn. The source may or may not contain a holder for the radioactive part and a grid or ring or similar surrounding the source to prevent cross contamination when the ^{212}Pb precursor isotope source is withdrawn from the container. In one embodiment it may be attached to a screw cap that can be used to close the container. The ^{212}Pb precursor isotope source can be isolated from the container by withdrawing the source into a cover. This will ensure that the source does not cross contaminate the inner walls of the container while the ^{212}Pb is extracted, and also limit risk of exposure to the user of the assembly. It is important that after a period of decay the ^{212}Pb precursor isotope source and the ^{212}Pb adsorbed onto the vial inner surfaces can be separated by withdrawing the ^{212}Pb precursor isotope source form the container, e.g. by replacing the screw cap of which the source is attached by a rod or similar with a standard gas tight screw cap. Thus, In one special embodiment is the ^{212}Pb precursor isotope source equipped with a retractable radioactive source that is withdrawn

into the cap similar to a "click pen system" or similar for isolating the source from the generator units interior surfaces and thus not require the disassembling and replacement of the cap (e.g. Figures 2 and 4). Thus, the second part of the assembly can comprise a piston that can be in open and closed positions. The second part of the assembly can also comprise a chamber with a gas tight o-ring seal. In one or more further embodiments the assembly comprises a gas and liquid tight lid or valve in the second part.

The second part of the assembly can, optionally, comprise a needle, rod or strip which may be supplied with a small ball of a material that can absorb radium or thorium including glass wool, quartz wool, mineral wool, metal, paper, cotton, stearate or another fatty acid, metal, cellulose, natural mineral, polymer, ion exchange resin, or other fibrous material. The composition of the holder of the precursor isotope should be chosen with care according to the known affinity of radon for various materials. A material that ^{228}Th and or ^{224}Ra has a good adsorption or absorption to and ^{220}Rn has a low affinity for would be suitable. The container can be made of a glass (including quartz), polymer and or metal, such as a glass vial, with a screw cap or similar, whereby the source is attached to the screw cap. The container (or assembly) can be a glass flask placed up-side down and with for example quartz wool with ^{224}Ra or ^{228}Th placed in the center of the inside of the cap. ^{212}Pb can be produced by unscrewing the flask standing up-side down from the cap with the source, and thereafter washing the interior of the flask with a solution to dissolve ^{212}Pb. The container can have a volume of 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml. The volume will depend on the use, where single use generally will be smaller and industrial batch containers will be larger.

Minimizing risk of cross contamination is important and the assembly has to be designed so that the ^{212}Pb precursor isotope source does not come into contact with the inner walls of the container. Thus, in one or more embodiments of the invention the container is substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The definition of substantially free depends on use of the ^{212}Pb produced in the assembly. In one or more embodiments of the invention is "substantially free" defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb. In one or more embodiments of the invention, the substantially free refers to the purity of ^{212}Pb vs ^{224}Ra in a solution from the walls of the container. This purity can be better than 95 %. This purity can be better than 98 %. This purity can be better than 99 %. This purity can be better than 99,5 %. This purity can be better than 99,8 %.

The container is surrounding, but not touching, the ^{212}Pb precursor isotope source. This should be made of an appropriate material, for example glass, plexiglass, metal, ceramics, polymer including polypropylene and Teflon or other materials suitable for allowing deposition of ^{220}Rn and/or ^{212}Pb on its inner walls and allowing ^{212}Pb to be dissolved when washed with a suitable solution for

further use in radiolabeling. A solution can be used to wash the inner walls of the container to extract radionuclides, mainly ^{212}Pb and progenies. It may be present during the ^{212}Pb production period in the assembly or be applied after the ^{212}Pb precursor isotope source has been removed or withdrawn. In one embodiment the solution and an acidic or alkaline solution that can be transferred and neutralized before use for administration to a patient. In one embodiment the solution may be water of a suitable purity for pharmaceutical use. Solution volume of 1 ul to 1 liter for single dosing, e.g. 100 ul to 10 ml, and 1 ul to 10 liter or higher for multiple dosing may be used.

The container may or may not contain a surface film on the inner surfaces or some liquid to assist in collecting the diffusion product. This surface film can for example be a coating. Size and volume may be in microliter to ml for single dosing units and in microliters to tens of liters or higher for multiple dosing. The inner walls of the container can be coated. This coating can ensure that ^{212}Pb settles in an optimal way. In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb. It is also possible that the inner walls are coated with one or more compounds where a complex with ^{212}Pb is needed. In one or more embodiments of the invention the inner walls of the container are coated with a chelator capable of chelating ^{212}Pb. This chelator can be TCMC or a variant hereof. The coating may be a film of salt or other suitable material on the inner walls.

In a special embodiment the container is washed directly with the reaction solution containing the complexing agent to yield a radiolabeling solution which after a suitable reaction time can be used directly for therapeutic purposes. In one embodiment the final product solution is autoclaved and or sterile filtered before administration to a subject in need thereof.

In one embodiment the assembly can be attached to a flushing and filtering circuit whereby when the source is retraced from the chamber a reservoir of a solution is connected and an outlet with a sterile filter and a syringe or vacuum pump is attached to flush the chamber and collect the flushing solution, *e.g.*, in similar fashion as for ^{99m}Tc-generators.

In general, surface ratios between precursor source holder and the collector chamber inner surfaces should be optimized so that as much as possible of the generated ^{212}Pb settles on the collector chamber surfaces. The surfaces may be smooth, or porous or may contain structures to increase surface area relative to the diffusion subunit, container or assembly.

The production can be a production period of 5 hours, 10, hours, 20 hours or more. Afterwards the source may be withdrawn from the chamber into a tube-shaped holder or similar with a gas and liquid tight lid in the bottom that closes when the source is completely withdrawn. This allows for addition of a washing solution, *e.g.*, by a syringe, or activation of a flushing and collecting circuit *e.g.* similar to that of a ^{99m}Tc generator.

In a special embodiment the single chamber diffusion unit has its ^{212}Pb precursor isotope source as a film on the inside surfaces of the assembly and has the ^{212}Pb collector unit (container) inserted into the source covered surfaces without touching these, *i.e.* a reverse configuration compared to what is shown in figure 2.

In another embodiment the diffusion generator is subject to temperature manipulation, either elevated or reduced temperature vs 20 °C.

The use of the invention for includes in the production of radiopharmaceuticals, medical devices and or standardization sources for ^{212}Pb. The assembly of the present invention can be used to generate a ^{212}Pb standard for calibrations.

In one or more embodiments of the invention is the assembly of the present invention comprised in kit with the ^{212}Pb precursor isotope source, and a solution containing a chelator, and a compound that for use in therapy. Such compound can be a nano- or microparticle. In one embodiment such a kit will contain a ^{212}Pb precursor isotope source, a solution for washing the inner walls of the container and a solution or dry form of a carrier compound, for example a chelator, micro- or nanoparticles.

Tables

Table 1. Main radiation properties of the ^{224}Ra series.

Radionuclide (half-life)	Alphas and betas (mean energy in MeV)	X-rays and gammas Energy and % abundance
^{224}Ra (3.6 days)	α 5.6	241 keV, 4.1%
^{220}Rn (55.6 s)	α 6.3	
^{216}Po (145 ms)	α 6.8	
^{212}Pb (10.6 h)	β 0.1	75 keV, 10.3% 77 keV, 17.1% 87 keV, 6.0% 90 keV, 1.5% 239 keV, 43.6% 300 keV, 3.3%
^{212}Bi (1 h)	α 6.1 × 0.36 (2.2 MeV effective[1]) β 0.7 × 0.64 (0.4 MeV effective)	727 keV, 6.7% (4.3% effective)
^{212}Po (299 ns) (64% branch)	α 8.8 (5.6 effective)	
^{208}Tl (3.1 min) (36% branch)	β 0.6 (0.2 MeV effective)	75 keV, 3.4% (1.2% effective) 511 keV, 22.6% (8.1% effective) 583 keV, 85.0% (30.6% effective) 860 keV, 12.5% (4.5% effective) 2615 keV, 99.8% (35.9% effective)

[1]Average per ^{224}Ra transformation due to branching. Only X-rays or gammas above 1% effective abundance accounted for. Adds up to a total effective energy of approximately 26.5 MeV of alpha of 0.7 MeV of beta per complete decay of a ^{224}Ra atom via progenies to a stable ^{208}Pb atom.

Table 2. A pure ^{212}Pb source with initial 100 MBq ^{212}Pb kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	23.1	4.4	0.92	0.192

Table 3. Lead-212 production from a source with initial 100 MBq ^{224}Ra kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	72.9	63.4	53.1
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	51.0	44.4	37.2

Table 4. Lead-212 production from a source with initial 100 MBq ^{224}Ra source emptied for ^{212}Pb every 24 h.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	58.2	48.1	39.8
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	40.7	33.7	27.9

The following figures and examples are provided below to illustrate the present invention. They are intended to be illustrative and are not to be construed as limiting in any way.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the decay of ^{232}Th to its progenies. The decay type (alpha or beta) is indicated and so is the half-lives. These half-lives are important because they dictate the decay rate and are therefore also key in deciding the optimal mix of isotopes as ^{212}Pb precursor isotope source for the production of ^{212}Pb.

Figure 2A shows a figure of the single chamber container assembly with the container (A), the a ^{212}Pb precursor isotope source (B) that generates the ^{220}Rn gas which is released into the single chamber container assembly and after decay settled as ^{212}Pb onto the inner walls of the container (C). The upper part of the single chamber container assembly (D) is the second part which comprises the ^{212}Pb precursor isotope source and in this case a cover/cap with a rod attached pointing towards the centre of the container thus enabling ^{212}Pb precursor isotope source release of ^{220}Rn into the container. Figure 2B shows a situation where the ^{212}Pb precursor isotope source (B) has been withdrawn into a gas tight seal that ensures that no ^{220}Rn is released into the container. The ^{212}Pb precursor isotope source can also be removed entirely from the assembly.

Figure 3 shows picture of a crude version of the generator system based on a 3 ml v-vial with an membrane inserted open top screw cap penetrated by a syringe tip (with position fixed by tape on top of screw cap) and with a strip of laboratory bench paper attached to the syringe tip (left picture shows the ^{212}Pb precursor isotope source and container). The ^{212}Pb precursor isotope source is placed onto the strip by a pipette before the screwcap with the source is carefully attached to the vial (right picture). It is very important that the source is not touching the vial when assembling and disassembling the unit to avoid cross-contamination.

Figure 4. An example of a single chamber diffusion generator for ^{212}Pb with a retractable source simplifying washout of ^{212}Pb from the inner surfaces by having syringe permeable zones on the lid supplied with septum, a syringe could be used for washing of the interior surfaces without radionuclide cross contamination when the unit is put in closed position.

Figure 5. Top picture shows a 100, 50 and 10 ml generator unit for ^{212}Pb production. Bottom pictures shows the cap with quartz wool in the center of the inner surface. The ^{212}Pb precursor nuclide solution can be placed onto the quartz wool and the flask mounted for up-side-down

storage to produce ^{212}Pb deposited on the flask' inner surface generated via ^{220}Rn diffusion from the precursor source material.

EXAMPLES

Example 1 - Calculation of the relative ^{212}Pb daughter nuclide level at various time points

Background. The development and use of pure ^{212}Pb in therapeutic radiopharmaceuticals is hampered by the short half-life (10.6 h) of the radionuclide making it almost impossible to produce a product in a centralized fashion and shipped to the end user. If ^{224}Ra is used as a short-term generator for ^{212}Pb the level of ^{212}Pb activity can be maintained essentially according to the half-life of ^{224}Ra, which is 3.6 days. The variation in ^{212}Pb level in a sealed source of pure ^{224}Ra is shown.

Method: The ingrowth of ^{212}Pb from a pure ^{224}Ra source were calculated using a universal activity calculator.

Results: Table 2 shows the amount of ^{212}Pb at various time points after the production of a pure (^{224}Ra-free) pharmaceutical solution and storage in a gas tight container. As can be seen the pure ^{212}Pb source rapidly decays and lose more than 75% per 24 h. Table 3 shows the amount of ^{212}Pb present in a sealed source of ^{224}Ra at the same time points. As can be seen the ^{212}Pb activity is maintained at a high level (> 50%) at least up to 96 h.

Table 4 shows the effect of "milking" a ^{224}Ra precursor-based generator for ^{212}Pb several times during a 96-h period.

The data also shows that significant amount of daughter nuclide is present within a relatively short time frame when starting with pure ^{224}Ra. It is noteworthy though that the ratio of ^{212}Pb to ^{224}Ra in the solution reaches 1 after 36 hours and thereafter gradually increases to about 1.1 of which is kept for the rest of the time until complete decay. In conclusion, using ^{224}Ra as a source for ^{212}Pb makes the logistic of centralized production and shipment to end users possible providing an easy way to extract the ^{212}Pb from ^{224}Ra exist.

Example 2 - Preparation of radionuclides and counting of radioactive samples

In the following, all work with the concentrated radioactive preparations including evaporation of solvent etc was performed in a glove-box. A source of ^{228}Th in 1 M HNO3 was acquired from a commercial supplier. Ac-resin was obtained from Eichrom Technologies LLC (Lisle, IL, USA) in the form of a pre-packed cartridge.

Radium-224 was made from ^{228}Th bound to Actinide resin (Eichrom Technologies, LLC) by eluting a column containing actinide resin with immobilized ^{228}Th with 1 M HCl. The eluate was purified on

a second Ac-resin column and the eluate evaporated to dryness using an evaporation vial with a cap with gas inlet and outlet placed in a heater block at approximately 110 ◦C and a gentle stream of nitrogen gas to evaporate of the solvent. When the evaporation vial was empty from solvent it was added 0.1 M HCl to dissolve the residue, typically 200-400 µl. Typically, more than 70% of the ^{224}Ra present in the ^{228}Th source could be extracted and purified using the described methods.

Radioactive samples were counted on a Cobra II Autogamma counter (Packard Instruments, Downer Grove, IL, USA). During extraction of ^{224}Ra from the ^{228}Th source, a CRC-25R dose calibrator (Capintec Inc., Ramsey, NJ, USA) was used.

Example 3 - Determining net count rate for ^{212}Pb in a ^{212}Pb/^{224}Ra mixture before radioactive equilibrium has been reached

After more than 3 days, i.e., “equilibrium” a sample kept gas tight will for practical purposes have 1.1 times ^{212}Pb vs ^{224}Ra.

In a gas tight unit regardless of whether ^{212}Pb is at or lower than equilibrium it can be assumed that this is reached after 3 days since surplus ^{212}Pb is reduced by 99% and the ingrowth of ^{212}Pb from ^{224}Ra is practically complete vs. “equilibrium”.

Using the Cobra II Autogamma counter with a counting window setting from 70-80 KeV gives mainly the ^{212}Pb with very little contribution from other radionuclides in the ^{224}Ra series. Radium-224 must be indirectly counted when the initial ^{212}Pb has vanished and equilibrium between ^{224}Ra and ^{212}Pb has been reached (after approximately 3 days). This indirect counting requires the sample to be stored in a relatively gas tight containers as otherwise the ^{220}Rn may escape preventing the radionuclide equilibrium of 1.1 between ^{212}Pb and ^{224}Ra to be reached.

Since sampling and counting may be separated by some time, the net count rate for ^{212}Pb can be adjusted for decay to determine the net ^{212}Pb count rate at the time of sampling. By storing ^{212}Pb samples for a week or longer and remeasure, the amount of ^{224}Ra contaminant can be determined as activity after about 110 hours of storage would not be ^{212}Pb but must be from longer lived precursor isotope.

Example 4 - A simplified single chamber (diffusion chamber generator) assembly for ^{212}Pb production (Figure 3).

A 3 ml v-vial with an open top cap. The open top cap was supplied with a membrane permeable by a syringe tip. A syringe tip was pushed through the membrane and fixed with tape on top to lock the position of the tip with regard to the open top cap. On the syringe tip vas placed a strip of

absorbent paper about 0.5 X 3 cm by inserting the syringe tip in two holes in the strip. The paper strip was added 2-40 ul ^{224}Ra solution. Thereafter the cap was placed carefully onto the v-vial while the syringe tip and radioactive strip were not to touch the inside of the v-vial. Thereafter the assembly was standing for various time to produce ^{212}Pb via ^{220}Rn diffusion from the strip to the space surrounding the strip. The ^{212}Pb tended to settle on the inner surfaces of the v-vial. Depending on the liquid volumes used for applying the ^{224}Ra source onto the strip, there may be some condensation of liquid due to evaporation/condensation of the liquid applied. Alternatively, the source could be dried before assembling the unit to avoid any solvent condensation on the v-vial inner surfaces.

Example 5A: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a paper strip.

Methods: The assembly was assembled with ^{224}Ra placed on the strip of the diffusion subunit inserted in a v-vial according to Figure 3, and was standing for 17.5 h or more to produce ^{220}Rn and ^{212}Pb. Production of ^{212}Pb evaluation of radiochemical purity of product. At the end of the production period the whole unit was measured on a Capintec dose calibrator. The product was evaluated by separating the source from the container and cap the latter with a gas tight screw cap and measure immediately in the Capintec dose calibrator. The purity of the product was determined by measuring the collector subunit again after a few days when all the ^{212}Pb had decayed but the presence of longer-lived predecessor nuclides ^{224}Ra and ^{228}Th would have been measurable. Results: Highly purified ^{212}Pb was collected in the collector subunit with a relevant yield of 65.6% (range 62.7-69.9% n=4) and with no measurable longer-lived precursor nuclides present (< 0.5%). In conclusion: The assembly was effective in producing and collecting purified ^{212}Pb in an easy manner without need for further purification.

Example 5B: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a parafilm strip. The experiment from 5A was repeated except that a parafilm strip was used instead of paper a strip to carry the precursor isotope source.

Results: The yield of ^{212}Pb on the inner surfaces of the collector subunit (vial or container) was found to be only 19.3%. In contrast a unit with paper strip run in parallel with exact same configuration and emanation period gave a yield of 63.9%. In conclusion, the material used for absorbing and holding the ^{212}Pb precursor isotope source could greatly affect the yield of ^{212}Pb on the collector subunit or container.

Example 6: Dissolving of ^{212}Pb from the container using a solution.

Methods: The collector vial was added 0.3-0.5 ml 0.1 M HCl which was gently swirled to contact the inner surfaces with the liquid and counted in the Capintec dose calibrator. Thereafter the liquid was transferred to an Eppendorf tube and measured in the Capitec dose calibrator. The extraction yield was 74.0 % (range 70.0-76.9%, n=3) when the collector subunit (3 ml v-vial), was washed one single time with 0.3 ml 0.1 M HCl. In conclusion, ^{212}Pb absorbed onto the surfaces of the container was rapidly and with good yield dissolved by a solution useful for radiopharmaceutical processing.

Example 7: Thin layer chromatography analyses

Thin layer chromatography (TLC) was performed using chromatography strips (model # 150-772, Biodex Medical Systems Inc, Shirley, NY, USA). A small beaker with about 0.5 ml of 0.9% NaCl was used to place strips with a sample spot in. To the strip was typically added 1-4 µl of sample at approximately 10% above the bottom of the strip. After the solvent front had moved to about 20% from the top of the strip, the strip was cut in half and each half was placed in a 5 ml test tube for counting. In this system radiolabeled antibody and free radionuclide does not migrate from the bottom half while radionuclide complexed with EDTA migrates to the upper half. A formulation buffer (FB) consisting of 7.5% human serum albumin and 1 mM EDTA in DPBS and adjusted to approximately pH 7 with NaOH was mixed with the radioconjugates in ratio 2:1 for at least 5 minutes before application to the strips to determine free radionuclide. It was verified that in a test solution with free ^{212}Pb was the radionuclide was completely (> 99%) complexed by the EDTA, when mixed with FB, and would travel to the upper half of the TLC strip.

Example 8: In situ chelation of ^{212}Pb in solutions.

Background: The labeling properties of the ^{212}Pb extracted with 0.1 M HCl from the containers was evaluated. Methods: A 10:1 ratio of ^{212}Pb in 0.1 M HCl and 5 M ammonium acetate was used before addition of the chelators, resulting in a pH range of 5 – 6 for the reactions. Reaction times of 15-30 minutes at 37 °C, were tested. For PSMA-617 solutions of 5 µg per 100 µl was labeled with good yield of 96.6% as determined by TLC. Also, TCMC-conjugated Herceptin antibody solution of approximately 1.0 mg/ml was labeled with pure ^{212}Pb with a good yield of 98.9%. In conclusion: Lead-212 produced with the assembly was readily complexed with small molecular and large

molecular conjugates indicating suitability for use in production of ^{212}Pb based radiopharmaceuticals.

Example 9 - Production of ^{212}Pb from the ^{224}Ra source when unit is kept sealed and emptied only at one time point

Table 3, lower row, shows the example of an output from a diffusion generator emptied after various time points after insertion of the source of 100 MBq of ^{224}Ra into the unit. As shown the generator gives a relatively stable output of ^{212}Pb for up to 96 h.

Example 10 - Production of ^{212}Pb from the ^{224}Ra source when unit is emptied once a day for four days e.g. if used for fractionated radionuclide therapy etc.

Table 4 shows the output when the assembly is "milked" once every 24 h. The combined output is a total of 151.5 MBq of ^{212}Pb when starting with a 100 MBq source. In conclusion, the one chamber assembly is suitable for single dose as well as fractionated dose production.

Example 11 - Example of an assembly with a retractable source (Figure 2 and Figure 4)

The materials used may be of glass (including quartz), polymer, metal, ceramic or other suitable materials for pharmaceutical containers. The rod in figure 2 (piston in figure 4) slides in a tube with o rings or similar at the top to secure gas tight seal. The valve at the bottom of the rod is gas and liquid tight in the closed position for the unit.

In the open position the source will be exposed inside the container and emanate ^{220}Rn and cause deposit of ^{212}Pb onto the inner surface. In closed position the source is sealed off from the container (Figure 2B) and the container surfaces can be contacted with a suitable solution to dissolve ^{212}Pb.

In one embodiment where the cap has syringe permeable membrane, a sterile syringe with a sterile solution is used to extract the ^{212}Pb without removing the cap. When such unit has been autoclaved before the extraction of ^{212}Pb, the complete procedure can be performed in an aseptic/sterile fashion.

Example 12. Precursor nuclide placed onto quartz wool in a ^{212}Pb single chamber generator.

Methods: A flasks as shown in figure 5, was used. Flask size could vary and typically 10-100 ml flasks were used. When used as a generator the flask was turned-up-side down. The cap was

removed and inside of the center of the cap was placed quarts or glass wool. Radium-224 in solution was placed on the quartz wool and the flask was mounted onto the cap without touching the quartz wool with the flask. The unit was kept tight and stored in up-side-down position for a period of time to produce ^{212}Pb from ingrowth. After typical one to a few days the flask was unscrewed from the cap while being held up-side-down and carefully removed from the cap without touching the quartz wool. The cap with the source was combined with another flask and stored up side down for further ^{212}Pb production. The unscrewed ^{212}Pb containing flask was added a solution of 0.5-2 ml of 0.1 M HCl and the ^{212}Pb extracted from the flask by washing the interior surfaces and collected for use.

Results: Typically, 50-70 percent of the ^{212}Pb activity produced was found in the flask and by carefully washing more than 90% of the ^{212}Pb activity could be collected in the washing solution. The produced ^{212}Pb had a very high purity with ^{224}Ra being as low as 10^{-4} vs ^{212}Pb in newly extracted solutions. The product was very suitable for use in labeling of chelator-containing proteins and small molecules giving very high labeling yields, typically above 97%.

In conclusion, the data showed that quartz wool was very suitable for holding a ^{224}Ra source indicating that quartz/glass/mineral wool, metal wool etc would be suitable for this purpose. It would be possible to use the flask/ quartz wool system in upright position also providing the quartz wool is adhered to the capsule, e.g. with glue, double-sided mounting tape etc. In the current example the flask was used up-side down and the quartz wool was not adhered, but just placed and kept by gravity in position inside the cap.

Example 13. Up-side-down flask system version of single the chamber generator.

Flask based diffusion generator for labeling with ^{212}Pb.

Lead-212 generate therapeutic high-LET radiation as it decays via short-lived alpha emitting daughters resulting in an average of one alpha particle per ^{212}Pb decay. The half-life of ^{212}Pb of 10.6 hours is a limitation to its use and fast and safe production and purification procedures are required. If a ready to use product was to be produced in a centralized production facility and shipped to the end user, the activity level would be reduced to less than 25% in one day. Lead-212 based radioimmunoconjugate has been in clinical testing against peritoneal cancer using ^{212}Pb separated from ^{224}Ra in a cation exchange column and eluted in mineral acid which has to be reconstituted before radiolabeling. This method requires a significant work effort, facilities, and equipment suitable for evaporation of mineral acids etc to work up the ^{212}Pb from the ^{224}Ra generator material. An alternative generator method was developed and tested based on ^{224}Ra absorbed onto quartz wool and placed inside the centered ring of a removable cap (the generator cap), in a generator chamber. The chamber consists of a glass bottle turned upside down and the

removable cap supports the ^{224}Ra labeled quartz wool (Figure 5). When ^{224}Ra decays, the short-lived ^{220}Rn emanates from the quartz wool and causes absorption of the longer-living decay product, ^{212}Pb, onto the interior surfaces of the flask. The flask can be removed from the cap without the glass coming in contact with the quartz wool. After removing the flask from the generator cap, the flask can be rinsed on the inside with 0.1 M HCl to dissolve the ^{212}Pb deposits whereby a highly purified ^{212}Pb solution is made. The operation and washout of the generator flask is made prior to radiolabeling of NG001. The purity of ^{212}Pb vs ^{224}Ra in the solution is, when the generator is operated in a correct manner (i.e. that the source does not come into contact with the walls), better than 99.8%. The generator can be re-used by attaching a new glass bottle to the generator cap and store for typically 1-2 days for the generation of fresh ^{212}Pb.

In summary, the generator method is easier to use and less time consuming compared with ion exchange-based generators. The generator may be re-used several times (although with a decreasing capacity due to radioactive decay depending of source half-life).

Example 14: Size of collector flask,

The flask sizes of 10, 50 and 100 ml was tested (Figure 5, upper part). ^{224}Ra was added to quarts wool placed in the cap of flasks placed upside down. The % ^{212}Pb on the flask compared with the theoretical yield varied from about 40% to 60%. It tended to be an advantage to use a larger flask to cap inner surface volume to obtain high yield. In conclusion, flasks with various sizes could be used for generator purposes but a relatively large flask vs. cap seemed to improve ^{212}Pb yield as relatively less would be lost due to absorption on the cap and the source material.

Example 15: Materials for holding the source.

To hold the source material in place inside the generator, e.g., in the inner cap center, Steel wool, glass wool, quartz wool was tested with ^{224}Ra sources. The materials are porous and fluffy and allows for diffusion. A volume of 100-150 microliter of ^{224}Ra in 0.1 M HCl was deposited onto the materials placed inside the caps of 100 ml flasks. After standing for 2-3 days or more, 52-64% of the ^{212}Pb compared to ^{224}Ra present in the generator would have settled on the glass surfaces, so all the three materials would work. i.e., quartz wool averaged of 5 tests, 59.9% (range 52.1-64.4%), glass wool 54.9% and steel wool 64.1% for one test each as compared to ^{224}Ra activity in the generator. In conclusion, several different materials could be used to hold the source in the one chamber diffusion generator.

Example 16: Sources.

The radionuclides ^{224}Ra and ^{228}Th were used as sources inside the generators. The ^{224}Ra -based generator could be used typically repeatedly up to a few weeks while the ^{228}Th -based unit could be used repeatedly for several months and deliver ^{212}Pb by simply switching the glass flask with an unused one and wash the first flask to produce a ^{212}Pb solution. Yield was not significantly reduced with repeated use except for the decay of the generator radionuclide. As long as the sources are centered inside the cap to avoid contact with the glass bottle, and flasks and caps are kept dry, cross contamination from source to the glass flask was minimal. In conclusion, the single chamber diffusion unit could be used repeatedly for producing ^{212}Pb with both ^{228}Th and ^{224}Ra as the sources. Lead-212 activity on the inner glass surfaces from ^{228}Th a source was found to be on average 49.3% (range 40.9%-66.7%) from four tests.

Example 17: Preparation including heating: To heat up flask before mounting onto the cap with the source material could be a way to produce reduced pressure in the generator. The flask was heated to 90 °C in a heat chamber for at least 15 minutes and then the flask and cap was screwed tightly together to be gas tight. The generator unit was thereafter stored at room temperature causing reduced inner pressure. After 1-4 days the chamber was opened and the ^{212}Pb activity on the glass flask was measured. The yield from four tests using ^{224}Ra on quartz wool was on average 68.1% (range 60.5%-75.9%, indicating improved yield compared with previous data for normal pressure flasks (average 59.9%). In conclusion, reduced chamber pressure may improve the yield of ^{212}Pb with the one chamber diffusion generator.

Example 18: Yield of ^{212}Pb in the washout solution.

A standard solution of 0.1 M HCl was used for extracting the ^{212}Pb trapped on the inner glass surface of 100 ml flasks. The washing solution was carefully shaken and swirled to cover the inside of the flasks for about 2 minutes and then 80% of the volume was taken out and measured and compared with the total count of the flask before the washing procedure. It was assumed that the 80% volumes should be divided by 0.8 to determine the total activity in the liquid. With 0.6 ml about 85% was extracted and with 1 ml 93% was extracted with similar washing effort. From ^{224}Ra based generator on average 86.1% (range 79.4%-93.4%) for 8 tests was extracted from the glass bottles. From ^{228}Th based generator on average 86.5% (range 84.5%-88.5%) for two tests was extracted from the glass bottles. In conclusion, ^{212}Pb trapped on the inner glass surfaces in the generators are easily extracted with 0.1 M HCl.

Example 19. Radiolabeling reactivity of solutions:

The TCMC-chelator-based molecule NG001 (Stenberg et al 2020) was used for testing ^{212}Pb labeling with the generator extracted ^{212}Pb. Lead-212 in 0.1 M HCl was added sodium acetate to adjust pH to about 5.5. Thereafter, NG001 was added to 10-20 micrograms per ml. After 30 minutes reaction on 37 °C using a Thermomixer (Eppendorf, Germany), samples were withdrawn and thin layer chromatography (TLC) was performed by mixing the samples 1:2 with 1 mM EDTMP in 7.5 % bovine serum albumin solution and let it stand for 5 minutes. Thereafter 1-5 microliter was applied onto a chromatography strip (model # 150-772, Biodex) and eluted with 0.9% NaCl solution in a beaker. When the liquid front reached the top of the strip, it was cut in two halves, each placed in a tube and counted separately in a Packard Cobra II gamma counter (Packard Instruments Co Inc, USA). The data showed that after 3 hours the activity of the bottom half would make up typically >99% indicating almost quantitative yield. Blind test without the NG001 but all the other compounds would give less than 3 % on the bottom half of the strip indicating good selectivity for the TLC test. In conclusion, the ^{212}Pb extracted from the generator flask showed excellent reactivity, indicating suitability for radiopharmaceutical use.

Example 20. Radiochemical purity of extracted solutions.

Lead-212 solutions were stored for 10 days or more and recounted for measuring ^{224}Ra. The ^{224}Ra activity was decay corrected back to time 0. The ^{224}Ra vs ^{212}Pb was determined to be on average 0.045% (range 0.01%-0.13%). In conclusion, the ^{212}Pb produced from the generator had high radiochemical purity relevant for pharmaceutical use.

CLAIMS

1. A method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of:

- providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source,
- connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided,
- allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, and/or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly,
- removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and
- obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

2. An assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

3. A single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

4. The method according to claim 1, the assembly according to claims 2-3, wherein the single chamber container assembly is gas tight.

5. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

6. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

7. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

8. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb activity is 0% to 114% of the ^{224}Ra precursor activity..

9. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb activity is 0% to 103% of the ^{228}Th precursor activity..

10. The method and the assembly according to any one of the proceeding claims, wherein the total amount of radioactivity in the single chamber container assembly is 1 kBq – 100 GBq.

11. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

12. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

13. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

14. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

15. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere that is made of a material suitable for application of a liquid.

16. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere which is made of material that is selected from the group consisting of quartz, glass, mineral, paper, plastic, metal, ceramic, and natural or synthetic fibers.

17. The method and the assembly according to claims 15-16, wherein a strip or sphere is attached to the second part, which comprises means for holding the sponge, the wool, the strip or the sphere, such as a rod.

18. The method and the assembly according to claim 17, wherein the second part comprises a syringe, or wherein the rod is the syringe.

19. The method and the assembly according to claim 18, wherein the syringe tip has been pushed through a rubber cap.

20. The method and the assembly according to any one of the proceeding claims, wherein the second part comprises a rod that is attached to the means for opening and closing the container.

21. The method and the assembly according to claim 20, wherein the means for opening and closing the container is a cap, cover or a lid.

22. The method and the assembly according to claim 21, wherein the cap, cover or a lid is made of a material selected from the group consisting of quartz, glass, mineral, rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

23. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

24. The method and the assembly according to any one of the proceeding claims, wherein the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

25. The method and the assembly according to claim 24, wherein the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

26. The method and the assembly according to claims 1-23, wherein the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

27. The method and the assembly according to any one of the proceeding claims, wherein volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

28. The method and the assembly according to any one of the proceeding claims, wherein substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % relative radioactivity.

29. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated.

30. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

31. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

32. The method and the assembly according to any one of the proceeding claims, wherein the container comprises an aqueous or an oil solution.

33. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a piston that can be in open and closed positions.

34. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a chamber with a gas tight o-ring seal.

35. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a gas and liquid tight lid or valve.

36. The method and the assembly according to any one of the proceeding claims, wherein the assembly is made by a glass flask placed up-side down and with quartz wool with ^{224}Ra or ^{228}Th placed in the center of the inside of the cap.

37. A method of obtaining a ^{212}Pb solution comprising obtaining a container or assembly comprising ^{212}Pb on the walls according to any of the previous claims, and subsequently collect the ^{212}Pb in a solution.

38. A method of obtaining a ^{212}Pb solution comprising obtaining a glass flask assembly according to claim 37, unscrewing the flask standing up-side down from the cap with the source, and thereafter washing the interior of the flask with a solution to dissolve ^{212}Pb.

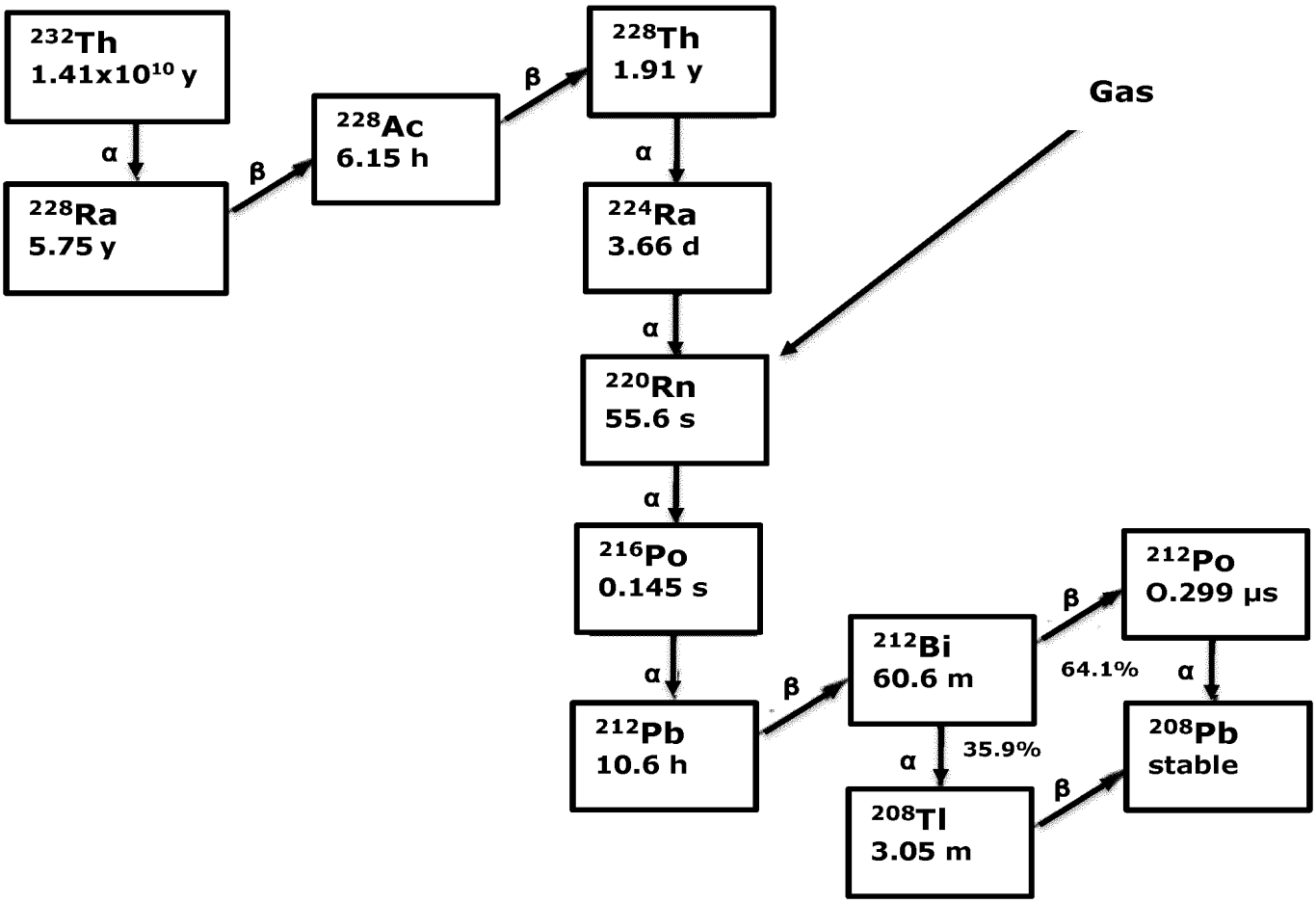

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α
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5.75 y
β
228Ac
6.15 h
β
228Th
1.91 y
α
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3.66 d
α
220Rn
55.6 s
Gas
α
216Po
0.145 s
α
212Pb
10.6 h
β
212Bi
60.6 m
β
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α
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β

Fig. 1

Figure 2A

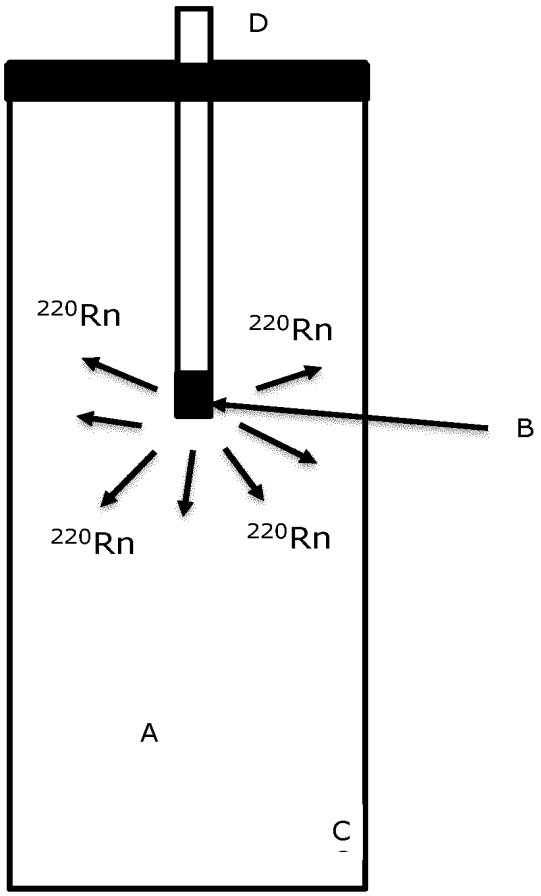


Figure 2B

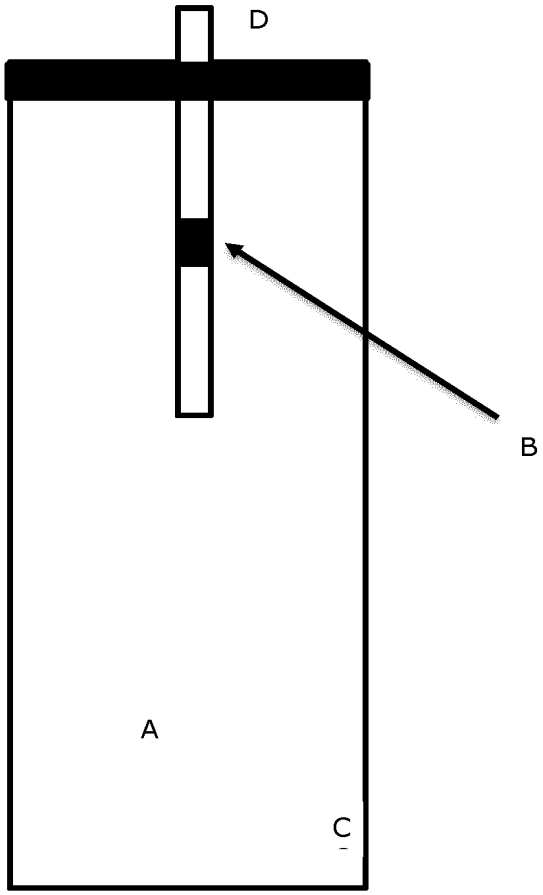


Fig 2

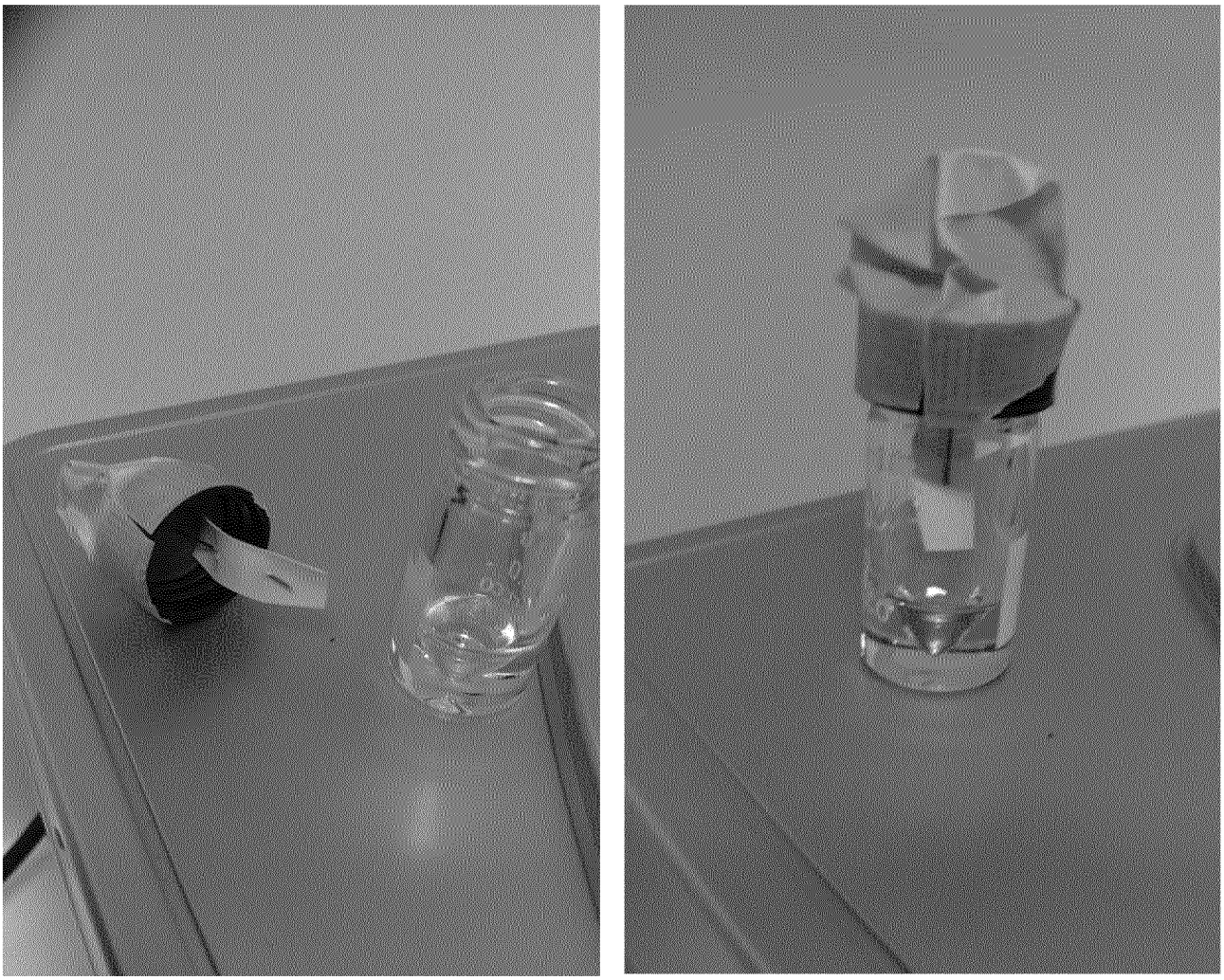


Fig 3

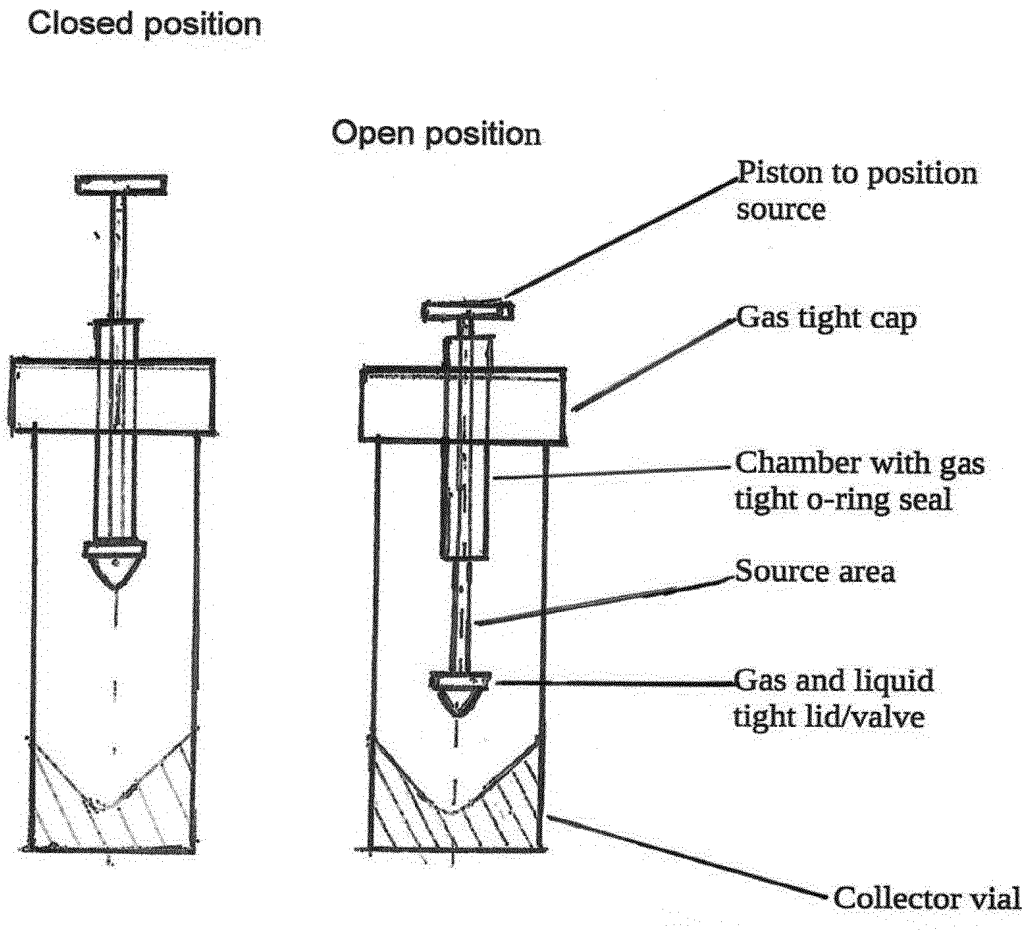

Closed position
Open position
Piston to position source
Gas tight cap
Chamber with gas tight o-ring seal
Source area
Gas and liquid tight lid/valve
Collector vial

Fig 4



Fig 5

PCT REQUEST

(Original in Electronic Form)

0	**For receiving Office use only**	
0-1	International Application No.	**PCT/EP2020/084701**
0-2	International Filing Date	**04 DEC 2020 (04.12.2020)**
0-3	Name of receiving Office and "PCT International Application"	**RO/EP**

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	CMS Online Filing Version CMS 1.80 MT/FOP 20020701/0.20.5.20
0-5	**Petition**	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	European Patent Office (EPO) (RO/EP)
0-7	**Applicant's or agent's file reference**	P2601WO00
I	**Title of Invention**	PRODUCTION OF HIGHLY PURIFIED 212PB
II	**Applicant**	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States
II-4	Name	SCIENCONS AS
II-5	Address	Gullhaugveien 7 NO-0484 Oslo Norway
II-6	State of nationality	NO
II-7	State of residence	NO
III-1	**Applicant and/or inventor**	
III-1-1	This person is	Inventor only
III-1-3	Inventor for	
III-1-4	Name (LAST, First)	LARSEN, Roy, H.
III-1-5	Address	Lunden 20 N-0598 Oslo Norway

PCT REQUEST

(Original in Electronic Form)

IV-1	**Agent or common representative; or address for correspondence**	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	Agent
IV-1-1	Name	AERA A/S
IV-1-2	Address	Gammel Kongevej 60, 18th floor DK-1850 Frederiksberg C Denmark
IV-1-3	Telephone No.	+4526166900
IV-1-5	e-mail	admin@aera-ip.com
IV-1-5(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	exclusively in electronic form (no paper notifications will be sent)
IV-1-6	Agent's registration No.	863
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	
VI-1	**Priority claim of earlier regional application**	
VI-1-1	Filing date	05 December 2019 (05.12.2019)
VI-1-2	Number	19213759.4
VI-1-3	Regional Office	EP
VI-2	**Priority claim of earlier regional application**	
VI-2-1	Filing date	29 April 2020 (29.04.2020)
VI-2-2	Number	20172038.0
VI-2-3	Regional Office	EP
VI-3	**Priority document request**	
	The International Bureau is requested to obtain from a digital library a certified copy of the earlier application(s) identified above as item(s), using, where applicable, the access code(s) indicated:	VI-1 Access code: 700F VI-2 Access code: 6BBF
VI-4	**Incorporation by reference :**	
	where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a), or an element or part of the description, claims or drawings referred to in Rule 20.5bis(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)

PCT REQUEST

(Original in Electronic Form)

VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	–	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	–	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	–	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	–	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	–	
IX	**Check list**	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	4	✓
IX-2	Description	25	✓
IX-3	Claims	5	✓
IX-4	Abstract	1	✓
IX-5	Drawings	5	✓
IX-6a	Sequence listing part of the description (also to be used for the purposes of international search)	–	–
IX-7	TOTAL	40	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	–	✓
IX-19	Other	Preconversion archive	✓
IX-20	**Figure of the drawings which should accompany the abstract**	1	
IX-21	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**	/PER LARSEN/	
X-1-1	Name	AERA A/S	
X-1-2	Name of signatory	(AERA A/S) Per Larsen *	* RO/EP
X-1-3	Capacity (if such capacity is not obvious from reading the request)	(Agent)	

PCT REQUEST

(Original in Electronic Form)

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	**04 DEC 2020 (04.12.2020)**
10-2	**Drawings:**	
10-2-1	Received	Received
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
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PRODUCTION OF HIGHLY PURIFIED 212PB

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
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Production of highly purified ^{212}Pb

FIELD

The present invention relates to a single chamber diffusion generator (assembly), assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

BACKGROUND

Assemblies for preparing or producing ^{212}Pb have previously been described and based on ^{228}Th bound to stearate in a chamber with another chamber for collecting the ^{212}Pb after ^{220}Rn has diffused from the first chamber (source chamber) to the second chamber (collector chamber).

In another system the $^{228}Th/^{224}Ra$ was extracted from one vessel with a pump generated airflow and $^{220}Rn/^{212}Pb$ collected in another vessel. The system consisted of an “air loop” for transportation of ^{220}Rn and a “fluid loop” for ^{212}Pb rinsing and after rinse collection. This is a quite complex system which is not suitable for shipment and handling, and the potential for leakage or inappropriate use in for example a hospital is significant.

In another system an emanator source is placed inside one chamber and a gas flow passes through and carry ^{220}Rn to another chamber where $^{220}Rn/^{212}Pb$ is collected. After some time, the carrier gas valve is closed, and the collection unit is added a liquid through a top valve and the liquid is collected through a bottom valve. This system is as well relatively complex. Both of these systems need significant work effort of skilled workers and relatively advanced lab equipment and space to operate.

Also, generator systems for ^{212}Pb not relying on ^{220}Rn emanation and diffusion has been presented previously. In one existing generator system ^{224}Ra is bound to ion exchange material and the ^{212}Pb extracted by elution with acid which must be evaporated before it can be used for radiolabeling in another existing system the ^{212}Pb in a solution with ^{224}Ra is used for labelling following the removal of ^{224}Ra by size exclusion purification. Both these methods are working but requires extra time for processing, more so for the first method than the second.

^{212}Pb has a half-life of only 10.6 h. This half-life makes the radioisotope idea for medical applications such as anti-cancer treatment because it acts on its target and without prolonged side effects from a long half-life. However, this feature also makes is difficult to use in a commercial setting involving centralized production and long-distance shipment to end users simply because it decays fast which gives lower yields over time.

Thus, a challenge for the current emanation and diffusion systems is transport distances which can reduce efficiency significantly due to decay of ^{220}Rn before reaching the collection vessels. For example, one system reported a total yield from a 3 days operation of 2.01 MBq ^{212}Pb collected compared from a ^{228}Th source of 7.05 MBq, *i.e.* less than 30% yield. Increasing the operation time did not increase the amount collected and the system was sensitive to the air flow rate.

There is a need for alpha-emitter therapeutics for biomedical applications. Lead-212 (^{212}Pb) is a beta-emitter that decays to short lived progenies producing alpha particles and can thus act as an alpha emitter generator *in vivo* useful in alpha emitter therapeutics.

This industry therefore needs an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

SUMMARY

An object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The described system may be termed a single chamber diffusion generator for ^{212}Pb.

In the following precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb i.e., ^{216}Po, ^{220}Rn, ^{224}Ra etc.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the

second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

In one or more embodiments of the invention the single chamber container assembly is gas tight.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the total amount of radioactivity in the single chamber container assembly is 1 kBq – 100 GBq.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose.

In one or more embodiments of the invention a strip or sphere is attached to the second part, which comprises means for holding the strip or sphere, such as a rod.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap.

In one or more embodiments of the invention the second part comprises a rod that is attached to the means for opening and closing the container.

In one or more embodiments of the invention the means for opening and closing the container is a cap, cover or a lid.

In one or more embodiments of the invention the cap, cover or a lid is made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

In one or more embodiments of the invention the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

In one or more embodiments of the invention the substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is less defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated. The coating may be a film of salt or other suitable material on the inner walls.

In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

DETAILED DESCRIPTION

The present inventors have in response to the need for a simpler, safer system with less size and transport distances to handle the short half-life of ^{220}Rn and ^{212}Pb, designed an assembly whereby the radon producing source is placed inside the collector chamber or container. Instead of using ^{228}Th only as a source is the present invention flexible and can able to use pure ^{224}Ra or a combination of ^{228}Th or ^{224}Ra as source, or even their precursor isotopes.

The assembly of the present inventions can be made very compact and very simple, allowing for a shippable and disposable ^{212}Pb-generator unit. In the present context is assembly, diffusion generator and system are used interchangeably. The described assembly or system may therefore be termed a single chamber diffusion generator for ^{212}Pb.

Thus, an object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the inner walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

An aspect of the invention relates to a method of obtaining a ^{212}Pb solution comprising obtaining the above container comprising ^{212}Pb on the walls and collect the ^{212}Pb in a solution. The ^{212}Pb can be collected in a solution that is in the container before the ^{212}Pb is generated or using a solution that is introduced to the container after the ^{212}Pb has been generated, and then collected. The collection can be done for example using a syringe.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

A huge advantage with the described assembly (or also defined herein as a system or a generator) is the ability to supply ^{212}Pb without the activity level is dictated by the short (10.6 h) half-life of ^{212}Pb. With the described system it is possible to produce a diffusion generator in a centralized production facility and ship it to the end user. A portable disposable generator could be made and shipped to *e.g.* a hospital from one end or the world to the other. For such a disposable unit, a pure ^{224}Ra (without ^{228}Th) is preferable as this would become inactive after 40-50 days approximately avoiding generation of long-lived radioactive waste. Such a diffusion source will steadily produce ^{220}Rn/^{212}Pb in a fashion dictated by the half-life of ^{224}Ra (Table 1 and Figure 1).

^{212}Pb is a member of the thorium natural radionuclide series and can be found in materials containing ^{232}Th ($t_{1/2}$=1.4x10^{10} years). The ^{212}Pb precursor can therefore be chosen based on the intended use. A precursor with longer half-life can be chosen to generate an assembly or system that that will act as a ^{212}Pb generator for continuous production over a longer period of time. Alternatively, an isotope with a shorter half-life be used is the intended use for example is at a hospital or similar where generation of long-lived radioactive waste can be problematic. Naturally a mix of different precursors will therefore also be relevant and also where specific assemblies are needed for the generation of a specific amount of ^{212}Pb over a specific period of time.

Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra. Thus, in the following ^{212}Pb precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb, *i.e.* ^{216}Po, ^{220}Rn, ^{224}Ra ^{228}Th, ^{228}Ac, ^{228}Ra, ^{232}Th.

The decay of these radioisotopes can be seen in figure 1 which clearly indicate the possibility of creating a ^{212}Pb precursor isotope source with different decay profiles and different combinations of precursor isotopes will be able to generate ^{212}Pb at different rates over different periods of time.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb

precursor isotope source is a mixture of ^{228}Th and ^{224}Ra. The source can also be each of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra individually, but due to the decay will a mixture naturally over time occur because ^{232}Th will decay to ^{228}Ra and so on. The key is that the gaseous ^{220}Rn is produced because it will diffuse from the source and later settle on the inner walls of the container as ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

The assembly working as a ^{212}Pb generator unit can be mass produced in a centralized production facility and shipped to end users for application in production of radiopharmaceuticals. It can also be adapted and used for large scale centralized production of ^{212}Pb. Thus, the amount of radioactivity in the assembly can adjusted according to its intended use. In one or more embodiments of the invention will the total amount of radioactivity in the single chamber container assembly therefore be 1 KBq – 100 GBq, such as 1 KBq – 10 MBq, such as 100 KBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq.

The ^{212}Pb precursor isotope source can be in different forms, sizes and shapes depending on the application type. Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$. The ^{212}Pb precursor isotope source can also be in a dry form or in a liquid solution, such as an aqueous solution or a dispersion. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH. The pH can be 1-14, such as pH 1-6, pH 2-6, pH 2-8, pH 4-8, pH 5-7, pH 6-8, pH 7-8, pH 7,2, pH 8-10, pH 8-12, or pH 10-14.

The assembly working as a generator system may be used for preparing single patient dosing or for multiple patient dosing, or even for industrial use. The amount of radioisotope can therefore be adjusted depending on the application of the assembly.

The ^{212}Pb precursor isotope source can be placed on the rod, either directly or on a strip attached to the rod, typically in a very small liquid volume. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid. Such liquid can be in the amount of 1 µl to 1 ml, such as 1 µl to 10 µl, such as 1 µl to 100 µl.

When the container, which can be a vial, can be empty or contain a small volume of liquid in the bottom, that is not touching the source. In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

It is important that the source does not drip or chip of in a fashion that causes cross contamination of the inner surfaces of the collector unit (container) with source material and that the source and source holder can be removed and or withdrawn from the collector without causing cross contamination by contact.

In one or embodiments the source is surrounded by a grid or encapsulated in a porous material to reduce risk of cross-contamination. This encapsulation can be a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

Thus, in one or more embodiments of the invention the container does or does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion. The container may comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source, and the gas permeable barrier impervious to the ^{212}Pb precursor isotope source can be in contact with the ^{212}Pb precursor isotope source. In one or more embodiments of the invention the single chamber container assembly is gas tight.

Figure 2 shows an example of the single chamber container assembly where the container (the first part) is connected with a cap and a rod attached to the cap is used to hold the ^{212}Pb precursor isotope source (the second part) without having this source touch an inner wall of the container during the entire process.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source can therefore be bound to a non-radioactive material, such as particles or a holding material. These can ensure that the source does not contaminate the container. The ^{212}Pb precursor isotope source can be deposited on a strip, sphere or a rod which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers. The strip or sphere can be attached to the second part or be contained or comprised in the second parts, which comprises means for holding the strip or sphere. Such means can for example be a rod.

In one or more embodiments of the invention the second part comprises, optionally, a rod that is attached to the means for opening and closing the container. The means for opening and closing the container can be a cap, cover or a lid which can be made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose ion exchange resin, natural mineral, polymer. Alternatively, the source is attached to a material

placed onto the cap with or without being adhered to the cap. If the cap is placed on the bottom, the source material can be simply placed onto the interior of the cap without touching the ^{212}Pb collector part and kept in place by gravitation. In such case the generator unit should be stored and handled in position whereby cap with the source is always kept at the bottom.

The means for opening and closing the container can comprise the ^{212}Pb precursor isotope source. The ^{212}Pb precursor isotope source can be placed on a sponge, a wool or another substance that is capable of keeping the ^{212}Pb precursor isotope source in the means for opening and closing the container. The wool can be a quartz wool. The wool can also be a mineral wool. The wool can also be a glass wool. The substance that is capable of keeping the ^{212}Pb precursor isotope source in the means for opening and closing the container can be attached by glue, double-sided mounting tape or other means for attachment.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe. The means for holding can be deposited on a strip or sphere which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers cellulose ion exchange resin, natural mineral, polymer.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap. An alternative design is where the second part is a rubber cap, or septum of another material permeable, and preferential self-sealing, with a syringe tip, with means for holding the ^{212}Pb precursor isotope source attached to the cap or to the inner walls of the container. In this case will user of the assembly be able to dissolve the ^{212}Pb from the inner walls of the container in an aqueous solution though a syringe that is pushed through the cap. The resulting ^{212}Pb in aqueous solution can afterwards be collected by the same syringe which will generate the option of working in a GMP environment which can be directly applied for patient use. Thus, in one embodiment the ^{212}Pb precursor isotope source be withdrawn into a capsule or similar allowing the container to be washed e.g., by using a solution transferred via a syringe through a rubber septum, without having to disassemble the two units. In another embodiment the assembly can be autoclaved, and the solution be of a physiological acceptable composition containing a chelator for disease targeting allowing withdrawal into a syringe and direct infusion with or without the use of a sterile syringe filter. In one embodiment the assembly including all subunits is autoclavable and with a syringe permeable zone on the cap allowing aseptic extraction of ^{212}Pb from the assembly.

After a few hours or days of operation the assembly with the ^{212}Pb precursor isotope source can be used for producing ^{212}Pb by retracting the ^{212}Pb precursor isotope source, e.g., by changing the cap with the attached ^{212}Pb precursor isotope source to a new cap without radioactivity and washing the inner surface with a suitable solution to dissolve surface deposited ^{212}Pb and

progenies. Since the ^{212}Pb solution is free from long lived predecessor radionuclides it can be used directly without further chemical processing to label carrier molecules for e.g. cancer therapy.

The ^{212}Pb precursor isotope source can associated with a needle, rod or a strip of a material of which ^{212}Pb precursor isotope source is attached to allow diffusion of ^{220}Rn. The source may or may not contain a holder for the radioactive part and a grid or ring or similar surrounding the source to prevent cross contamination when the ^{212}Pb precursor isotope source is withdrawn from the container. In one embodiment it may be attached to a screw cap that can be used to close the container. The ^{212}Pb precursor isotope source can be isolated from the container by withdrawing the source into a cover. This will ensure that the source does not cross contaminate the inner walls of the container while the ^{212}Pb is extracted, and also limit risk of exposure to the user of the assembly. It is important that after a period of decay the ^{212}Pb precursor isotope source and the ^{212}Pb adsorbed onto the vial inner surfaces can be separated by withdrawing the ^{212}Pb precursor isotope source form the container, e.g. by replacing the screw cap of which the source is attached by a rod or similar with a standard gas tight screw cap. Thus, In one special embodiment is the ^{212}Pb precursor isotope source equipped with a retractable radioactive source that is withdrawn into the cap similar to a “click pen system” or similar for isolating the source from the generator units interior surfaces and thus not require the disassembling and replacement of the cap (e.g. Figures 2 and 4). Thus, the second part of the assembly can comprise a piston that can be in open and closed positions. The second part of the assembly can also comprise a chamber with a gas tight o-ring seal. In one or more further embodiments the assembly comprises a gas and liquid tight lid or valve in the second part.

The second part of the assembly can, optionally, comprise a needle, rod or strip which may be supplied with a small ball of a material that can absorb radium or thorium including glass wool, quartz wool, mineral wool, metal, paper, cotton, stearate or another fatty acid, metal, cellulose, natural mineral, polymer, ion exchange resin, or other fibrous material. The composition of the holder of the precursor isotope should be chosen with care according to the known affinity of radon for various materials. A material that ^{228}Th and or ^{224}Ra has a good adsorption or absorption to and ^{220}Rn has a low affinity for would be suitable. The container can be made of a glass (including quartz), polymer and or metal, such as a glass vial, with a screw cap or similar, whereby the source is attached to the screw cap.

The container can have a volume of 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml. The volume will depend on the use, where single use generally will be smaller and industrial batch containers will be larger.

Minimizing risk of cross contamination is important and the assembly has to be designed so that the ^{212}Pb precursor isotope source does not come into contact with the inner walls of the container.

Thus, in one or more embodiments of the invention the container is substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The definition of substantially free depends on use of the ^{212}Pb produced in the assembly. In one or more embodiments of the invention is "substantially free" defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb.

The container is surrounding, but not touching, the ^{212}Pb precursor isotope source. This should be made of an appropriate material, for example glass, plexiglass, metal, ceramics, polymer including polypropylene and Teflon or other materials suitable for allowing deposition of ^{220}Rn and/or ^{212}Pb on its inner walls and allowing ^{212}Pb to be dissolved when washed with a suitable solution for further use in radiolabeling. A solution can be used to wash the inner walls of the container to extract radionuclides, mainly ^{212}Pb and progenies. It may be present during the ^{212}Pb production period in the assembly or be applied after the ^{212}Pb precursor isotope source has been removed or withdrawn. In one embodiment the solution and an acidic or alkaline solution that can be transferred and neutralized before use for administration to a patient. In one embodiment the solution may be water of a suitable purity for pharmaceutical use. Solution volume of 1 ul to 1 liter for single dosing, e.g. 100 ul to 10 ml, and 1 ul to 10 liter or higher for multiple dosing may be used.

The container may or may not contain a surface film on the inner surfaces or some liquid to assist in collecting the diffusion product. This surface film can for example be a coating. Size and volume may be in microliter to ml for single dosing units and in microliters to tens of liters or higher for multiple dosing. The inner walls of the container can be coated. This coating can ensure that ^{212}Pb settles in an optimal way. In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb. It is also possible that the inner walls are coated with one or more compounds where a complex with ^{212}Pb is needed. In one or more embodiments of the invention the inner walls of the container are coated with a chelator which is TCMC or a variant hereof. The coating may be a film of salt or other suitable material on the inner walls.

In a special embodiment the container is washed directly with the reaction solution containing the complexing agent to yield a radiolabeling solution which after a suitable reaction time can be used directly for therapeutic purposes. In one embodiment the final product solution is autoclaved and or sterile filtered before administration to a subject in need thereof.

In one embodiment the assembly can be attached to a flushing and filtering circuit whereby when the source is retraced from the chamber a reservoir of a solution is connected and an outlet with a sterile filter and a syringe or vacuum pump is attached to flush the chamber and collect the flushing solution, *e.g.*, in similar fashion as for ^{99m}Tc-generators.

In general, surface ratios between precursor source holder and the collector chamber inner surfaces should be optimized so that as much as possible of the generated ^{212}Pb settles on the collector chamber surfaces. The surfaces may be smooth, or porous or may contain structures to increase surface area relative to the diffusion subunit, container or assembly.

The production can be a production period of 5 hours, 10, hours, 20 hours or more. Afterwards the source may be withdrawn from the chamber into a tube-shaped holder or similar with a gas and liquid tight lid in the bottom that closes when the source is completely withdrawn. This allows for addition of a washing solution, *e.g.*, by a syringe, or activation of a flushing and collecting circuit *e.g.* similar to that of a ^{99m}Tc generator.

In a special embodiment the single chamber diffusion unit has its ^{212}Pb precursor isotope source as a film on the inside surfaces of the assembly and has the ^{212}Pb collector unit (container) inserted into the source covered surfaces without touching these, *i.e.* a reverse configuration compared to what is shown in figure 2.

In another embodiment the diffusion generator is subject to temperature manipulation, either elevated or reduced temperature vs 20 oC.

The use of the invention for includes in the production of radiopharmaceuticals, medical devices and or standardization sources for ^{212}Pb. The assembly of the present invention can be used to generate a ^{212}Pb standard for calibrations.

In one or more embodiments of the invention is the assembly of the present invention comprised in kit with the ^{212}Pb precursor isotope source, and a solution containing a chelator, and a compound that for use in therapy. Such compound can be a nano- or microparticle. In one embodiment such a kit will contain a ^{212}Pb precursor isotope source, a solution for washing the inner walls of the container and a solution or dry form of a carrier compound, for example a chelator, micro- or nanoparticles.

Tables

Table 1. Main radiation properties of the ^{224}Ra series.

Radionuclide (half-life)	Alphas and betas (mean energy in MeV)	X-rays and gammas Energy and % abundance
^{224}Ra (3.6 days)	α 5.6	241 keV, 4.1%
^{220}Rn (55.6 s)	α 6.3	
^{216}Po (145 ms)	α 6.8	
^{212}Pb (10.6 h)	β 0.1	75 keV, 10.3% 77 keV, 17.1% 87 keV, 6.0% 90 keV, 1.5% 239 keV, 43.6%

		300 keV, 3.3%
^{212}Bi (10.6 h)	α 6.1 × 0.36 (2.2 MeV effective[1]) β 0.7 × 0.64 (0.4 MeV effective)	727 keV, 6.7% (4.3% effective)
^{212}Po (299 ns) (64% branch)	α 8.8 (5.6 effective)	
^{208}Tl (3.1 min) (36% branch)	β 0.6 (0.2 MeV effective)	75 keV, 3.4% (1.2% effective) 511 keV, 22.6% (8.1% effective) 583 keV, 85.0% (30.6% effective) 860 keV, 12.5% (4.5% effective) 2615 keV, 99.8% (35.9% effective)

[1]Average per ^{224}Ra transformation due to branching. Only X-rays or gammas above 1% effective abundance accounted for. Adds up to a total effective energy of approximately 26.5 MeV of alpha of 0.7 MeV of beta per complete decay of a ^{224}Ra atom via progenies to a stable ^{208}Pb atom.

Table 2. A pure ^{212}Pb source with initial 100 MBq ^{212}Pb kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	23.1	4.4	0.92	0.192

Table 3. Lead-212 production from a source with initial 100 MBq ^{224}Ra kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	72.9	63.4	53.1
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	51.0	44.4	37.2

Table 4. Lead-212 production from a source with initial 100 MBq ^{224}Ra source emptied for ^{212}Pb every 24 h.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	58.2	48.1	39.8
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	40.7	33.7	27.9

The following figures and examples are provided below to illustrate the present invention. They are intended to be illustrative and are not to be construed as limiting in any way.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the decay of ^{232}Th to its progenies. The decay type (alpha or beta) is indicated and so is the half-lives. These half-lives are important because they dictate the decay rate and are therefore also key in deciding the optimal mix of isotopes as ^{212}Pb precursor isotope source for the production of ^{212}Pb.

Figure 2A shows a figure of the single chamber container assembly with the container (A), the a ^{212}Pb precursor isotope source (B) that generates the ^{220}Rn gas which is released into the single chamber container assembly and after decay settled as ^{212}Pb onto the inner walls of the container (C). The upper part of the single chamber container assembly (D) is the second part which comprises the ^{212}Pb precursor isotope source and in this case a cover/cap with a rod attached pointing towards the centre of the container thus enabling ^{212}Pb precursor isotope source release of ^{220}Rn into the container. Figure 2B shows a situation where the ^{212}Pb precursor isotope source (B) has been withdrawn into a gas tight seal that ensures that no ^{220}Rn is released into the container. The ^{212}Pb precursor isotope source can also be removed entirely from the assembly.

Figure 3 shows picture of a crude version of the generator system based on a 3 ml v-vial with an membrane inserted open top screw cap penetrated by a syringe tip (with position fixed by tape on top of screw cap) and with a strip of laboratory bench paper attached to the syringe tip (left picture shows the ^{212}Pb precursor isotope source and container). The ^{212}Pb precursor isotope source is placed onto the strip by a pipette before the screwcap with the source is carefully attached to the vial (right picture). It is very important that the source is not touching the vial when assembling and disassembling the unit to avoid cross-contamination.

Figure 4. An example of a single chamber diffusion generator for ^{212}Pb with a retractable source simplifying washout of ^{212}Pb from the inner surfaces by having syringe permeable zones on the lid supplied with septum, a syringe could be used for washing of the interior surfaces without radionuclide cross contamination when the unit is put in closed position.

Figure 5. Top picture shows a 100, 50 and 10 ml generator unit for ^{212}Pb production. Bottom pictures shows the cap with quartz wool in the center of the inner surface. The ^{212}Pb precursor nuclide solution can be placed onto the quartz wool and the flask mounted for up-side-down

storage to produce ^{212}Pb deposited on the flask' inner surface generated via ^{220}Rn diffusion from the precursor source material.

EXAMPLES

Example 1 - Calculation of the relative ^{212}Pb daughter nuclide level at various time points

Background. The development and use of pure ^{212}Pb in therapeutic radiopharmaceuticals is hampered by the short half-life (10.6 h) of the radionuclide making it almost impossible to produce a product in a centralized fashion and shipped to the end user. If ^{224}Ra is used as a short-term generator for ^{212}Pb the level of ^{212}Pb activity can be maintained essentially according to the half-life of ^{224}Ra, which is 3.6 days. The variation in ^{212}Pb level in a sealed source of pure ^{224}Ra is shown.

Method: The ingrowth of ^{212}Pb from a pure ^{224}Ra source were calculated using a universal activity calculator.

Results: Table 2 shows the amount of ^{212}Pb at various time points after the production of a pure ^{224}Ra pharmaceutical solution and storage in a gas tight container. As can be seen the pure ^{212}Pb source rapidly decays and lose more than 75% per 24 h. Table 3 shows the amount of ^{212}Pb present in a sealed source of ^{224}Ra at the same time points. As can be seen the ^{212}Pb activity is maintained at a high level (> 50%) at least up to 96 h.

Table 4 shows the effect of “milking” a ^{224}Ra precursor-based generator for ^{212}Pb several times during a 96-h period. Notice that the total combined output of ^{212}Pb can exceed the source radioactivity by more than a factor of 1.5 when ^{212}Pb is removed once a day for up to 4 days.

The data also shows that significant amount of daughter nuclide is present within a relatively short time frame when starting with pure ^{224}Ra. It is noteworthy though that the ratio of ^{212}Pb to ^{224}Ra in the solution reaches 1 after 36 hours and thereafter gradually increases to about 1.1 of which is kept for the rest of the time until complete decay. In conclusion, using ^{224}Ra as a source for ^{212}Pb makes the logistic of centralized production and shipment to end users possible providing an easy way to extract the ^{212}Pb from ^{224}Ra exist.

Example 2 - Preparation of radionuclides and counting of radioactive samples

In the following, all work with the concentrated radioactive preparations including evaporation of solvent etc was performed in a glove-box. A source of ^{228}Th in 1 M HNO3 was acquired from a commercial supplier. Ac-resin was obtained from Eichrom Technologies LLC (Lisle, IL, USA) in the form of a pre-packed cartridge.

Radium-224 was made from ^{228}Th bound to Actinide resin (Eichrom Technologies, LLC) by eluting a column containing actinide resin with immobilized ^{228}Th with 1 M HCl. The eluate was purified on a second Ac-resin column and the eluate evaporated to dryness using an evaporation vial with a cap with gas inlet and outlet placed in a heater block at approximately 110 ◦C and a gentle stream of nitrogen gas to evaporate of the solvent. When the evaporation vial was empty from solvent it was added 0.1 M HCl to dissolve the residue, typically 200-400 µl. Typically, more than 70% of the ^{224}Ra present in the ^{228}Th source could be extracted and purified using the described methods.

Radioactive samples were counted on a Cobra II Autogamma counter (Packard Instruments, Downer Grove, IL, USA). During extraction of ^{224}Ra from the ^{228}Th source, a CRC-25R dose calibrator (Capintec Inc., Ramsey, NJ, USA) was used.

Example 3 - Determining net count rate for ^{212}Pb in a ^{212}Pb/^{224}Ra mixture before radioactive equilibrium has been reached

After more than 3 days, i.e., “equilibrium” a sample will for practical purposes have 1.1 times ^{212}Pb vs ^{224}Ra.

Regardless of whether ^{212}Pb is higher or lower than equilibrium it can be assumed that this is reached after 3 days since surplus ^{212}Pb is reduced by 99% and the ingrowth of ^{212}Pb from ^{224}Ra is practically complete vs. “equilibrium”.

Using the Cobra II Autogamma counter with a counting window setting from 70-80 KeV gives mainly the ^{212}Pb with very little contribution from other radionuclides in the ^{224}Ra series. Radium-224 must be indirectly counted when the initial ^{212}Pb has vanished and equilibrium between ^{224}Ra and ^{212}Pb has been reached (after approximately 3 days). This indirect counting requires the sample to be stored in a relatively gas tight containers as otherwise the ^{220}Rn may escape preventing the radionuclide equilibrium of 1.1 between ^{212}Pb and ^{224}Ra to be reached.

Since sampling and counting may be separated by some time, the net count rate for ^{212}Pb can be adjusted for decay to determine the net ^{212}Pb count rate at the time of sampling. By storing ^{212}Pb samples for a week or longer and remeasure, the amount of ^{224}Ra contaminant can be determined as activity after about 110 hours of storage would not be ^{212}Pb but must be from longer lived precursor isotope.

Example 4 - A simplified single chamber (diffusion chamber generator) assembly for ^{212}Pb production (Figure 3).

A 3 ml v-vial with an open top cap. The open top cap was supplied with a membrane permeable by a syringe tip. A syringe tip was pushed through the membrane and fixed with tape on top to lock the position of the tip with regard to the open top cap. On the syringe tip vas placed a strip of absorbent paper about 0.5 X 3 cm by inserting the syringe tip in two holes in the strip. The paper strip was added 2-40 ul ^{224}Ra solution. Thereafter the cap was placed carefully onto the v-vial while the syringe tip and radioactive strip were not to touch the inside of the v-vial. Thereafter the assembly was standing for various time to produce ^{212}Pb via ^{220}Rn diffusion from the strip to the space surrounding the strip. The ^{212}Pb tended to settle on the inner surfaces of the v-vial. Depending on the liquid volumes used for applying the ^{224}Ra source onto the strip, there may be some condensation of liquid due to evaporation/condensation of the liquid applied. Alternatively, the source could be dried before assembling the unit to avoid any solvent condensation on the v-vial inner surfaces.

Example 5A: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a paper strip.

Methods: The assembly was assembled with ^{224}Ra placed on the strip of the diffusion subunit inserted in a v-vial according to Figure 3, and was standing for 17.5 h or more to produce ^{220}Rn and ^{212}Pb. Production of ^{212}Pb evaluation of radiochemical purity of product. At the end of the production period the whole unit was measured on a Capintec dose calibrator. The product was evaluated by separating the source from the container and cap the latter with a gas tight screw cap and measure immediately in the Capintec dose calibrator. The purity of the product was determined by measuring the collector subunit again after a few days when all the ^{212}Pb had decayed but the presence of longer-lived predecessor nuclides ^{224}Ra and ^{228}Th would have been measurable. Results: Highly purified ^{212}Pb was collected in the collector subunit with a relevant yield of 65.6% (range 62.7-69.9% n=4) and with no measurable longer-lived precursor nuclides present (< 0.5%). In conclusion: The assembly was effective in producing and collecting purified ^{212}Pb in an easy manner without need for further purification.

Example 5B: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a parafilm strip. The experiment from 5A was repeated except that a parafilm strip was used instead of paper a strip to carry the precursor isotope source.

Results: The yield of ^{212}Pb on the inner surfaces of the collector subunit (vial or container) was found to be only 19.3%. In contrast a unit with paper strip run in parallel with exact same configuration and emanation period gave a yield of 63.9%. In conclusion, the material used for absorbing and holding the ^{212}Pb precursor isotope source could greatly affect the yield of ^{212}Pb on the collector subunit or container.

Example 6: Dissolving of ^{212}Pb from the container using a solution.

Methods: The collector vial was added 0.3-0.5 ml 0.1 M HCl which was gently swirled to contact the inner surfaces with the liquid and counted in the Capintec dose calibrator. Thereafter the liquid was transferred to an Eppendorf tube and measured in the Capitec dose calibrator. The extraction yield was 740 % (range 70.0-76.9%, n=3) when the collector subunit (3 ml v-vial), was washed one single time with 0.3 ml 0.1 M HCl. In conclusion, ^{212}Pb absorbed onto the surfaces of the container was rapidly and with good yield dissolved by a solution useful for radiopharmaceutical processing.

Example 7: Thin layer chromatography analyses

Thin layer chromatography (TLC) was performed using chromatography strips (model # 150-772, Biodex Medical Systems Inc, Shirley, NY, USA). A small beaker with about 0.5 ml of 0.9% NaCl was used to place strips with a sample spot in. To the strip was typically added 1-4 µl of sample at approximately 10% above the bottom of the strip. After the solvent front had moved to about 20% from the top of the strip, the strip was cut in half and each half was placed in a 5 ml test tube for counting. In this system radiolabeled antibody and free radionuclide does not migrate from the bottom half while radionuclide complexed with EDTA migrates to the upper half. A formulation buffer (FB) consisting of 7.5% human serum albumin and 1 mM EDTA in DPBS and adjusted to approximately pH 7 with NaOH was mixed with the radioconjugates in ratio 2:1 for at least 5 minutes before application to the strips to determine free radionuclide. It was verified that in a test solution with free ^{212}Pb was the radionuclide was completely (> 99%) complexed by the EDTA, when mixed with FB, and would travel to the upper half of the TLC strip.

Example 8: In situ chelation of ^{212}Pb in solutions.

Background: The labeling properties of the ^{212}Pb extracted with 0.1 M HCl from the containers was evaluated. Methods: A 10:1 ratio of ^{212}Pb in 0.1 M HCl and 5 M ammonium acetate was used before addition of the chelators, resulting in a pH range of 5 – 6 for the reactions. Reaction times of

15-30 minutes at 37 °C, were tested. For PSMA-617 solutions of 5 ug per 100 ul was labeled with good yield of 96.6% as determined by TLC. Also, TCMC-conjugated Herceptin antibody solution of approximately 1.0 mg/ml was labeled with pure ^{212}Pb with a good yield of 98.9%. In conclusion: Lead-212 produced with the assembly was readily complexed with small molecular and large molecular conjugates indicating suitability for use in production of ^{212}Pb based radiopharmaceuticals.

Example 9 - Production of ^{212}Pb from the ^{224}Ra source when unit is kept sealed and emptied only at one time point

Table 3, lower row, shows the example of an output from a diffusion generator emptied after various time points after insertion of the source of 100 MBq of ^{224}Ra into the unit. As shown the generator gives a relatively stable output of ^{212}Pb for up to 96 h.

Example 10 - Production of ^{212}Pb from the ^{224}Ra source when unit is emptied once a day for four days e.g. if used for fractionated radionuclide therapy etc.

Table 4 shows the output when the assembly is “milked” once every 24 h. The combined output is a total of 151.5 MBq of ^{212}Pb when starting with a 100 MBq source. In conclusion, the one chamber assembly is suitable for single dose as well as fractionated dose production.

Example 11 - Example of an assembly with a retractable source (Figure 2 and Figure 4)

The materials used may be of glass (including quartz), polymer, metal, ceramic or other suitable materials for pharmaceutical containers. The rod in figure 2 (piston in figure 4) slides in a tube with o rings or similar at the top to secure gas tight seal. The valve at the bottom of the rod is gas and liquid tight in the closed position for the unit.

In the open position the source will be exposed inside the container and emanate ^{220}Rn and cause deposit of ^{212}Pb onto the inner surface. In closed position the source is sealed off from the container (Figure 2B) and the container surfaces can be contacted with a suitable solution to dissolve ^{212}Pb.

In one embodiment where the cap has syringe permeable membrane, a sterile syringe with a sterile solution is used to extract the ^{212}Pb without removing the cap. When such unit has been autoclaved before the extraction of ^{212}Pb, the complete procedure can be performed in an aseptic/sterile fashion.

Example 12. Precursor nuclide placed onto quartz wool in a ^{212}Pb single chamber generator.

Methods: A flasks as shown in figure 5, was used. Flask size could vary and typically 10-100 ml flasks were used. When used as a generator the flask was turned-up-side down. The cap was removed and inside of the center of the cap was placed quarts or glass wool. Radium-224 in solution was placed on the quartz wool and the flask was mounted onto the cap without touching the quartz wool with the flask. The unit was kept tight and stored in up-side-down position for a period of time to produce ^{212}Pb from ingrowth. After typical one to a few days the flask was unscrewed from the cap while being held up-side-down and carefully removed from the cap without touching the quartz wool. The cap with the source was combined with another flask and stored up side down for further ^{212}Pb production. The ^{212}Pb containing flask was added a solution of 0.5-2 ml of 0.1 M HCl and the ^{212}Pb extracted from the flask by washing the interior surfaces and collected for use.

Results: Typically, 50-70 percent of the ^{212}Pb activity produced was found in the flask and by carefully washing more than 90% of the ^{212}Pb activity could be collected in the washing solution. The produced ^{212}Pb had a very high purity with ^{224}Ra being below 10^{-5} vs ^{212}Pb in newly extracted solutions. The product was very suitable for use in labeling of chelator-containing proteins and small molecules giving very high labeling yields, typically above 97%.

In conclusion, the data showed that quartz wool was very suitable for holding a ^{224}Ra source indicating that quartz/glass/mineral wool, metal wool etc would be suitable for this purpose. It would be possible to use the flask/ quartz wool system in upright position also providing the quartz wool is adhered to the capsule, e.g. with glue, double-sided mounting tape etc. In the current example the flask was used up-side down and the quartz wool was not adhered, but just placed and kept by gravity in position inside the cap.

CLAIMS

1. A method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of:

- providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source,
- connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided,
- allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly,
- removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and
- obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

2. An assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

3. A single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

4. The method according to claim 1, the assembly according to claims 2-3, wherein the single chamber container assembly is gas tight.

5. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

6. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

7. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

8. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

9. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

10. The method and the assembly according to any one of the proceeding claims, wherein the total amount of radioactivity in the single chamber container assembly is 1 KBq – 100 GBq.

11. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

12. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

13. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

14. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

15. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere that is made of a material suitable for application of a liquid.

16. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere which is made of material that is selected from the group consisting of quartz, glass, mineral, paper, plastic, metal, ceramic, and natural or synthetic fibers.

17. The method and the assembly according to claims 15-16, wherein a strip or sphere is attached to the second part, which comprises means for holding the sponge, the wool, the strip or the sphere, such as a rod.

18. The method and the assembly according to claim 17, wherein the second part comprises a syringe, or wherein the rod is the syringe.

19. The method and the assembly according to claim 18, wherein the syringe tip has been pushed through a rubber cap.

20. The method and the assembly according to any one of the proceeding claims, wherein the second part comprises a rod that is attached to the means for opening and closing the container.

21. The method and the assembly according to claim 20, wherein the means for opening and closing the container is a cap, cover or a lid.

22. The method and the assembly according to claim 21, wherein the cap, cover or a lid is made of a material selected from the group consisting of quartz, glass, mineral, rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

23. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

24. The method and the assembly according to any one of the proceeding claims, wherein the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

25. The method and the assembly according to claim 24, wherein the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

26. The method and the assembly according to claims 1-23, wherein the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

27. The method and the assembly according to any one of the proceeding claims, wherein volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

28. The method and the assembly according to any one of the proceeding claims, wherein substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is less defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % relative radioactivity.

29. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated.

30. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

31. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

32. The method and the assembly according to any one of the proceeding claims, wherein the container comprises an aqueous or an oil solution.

33. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a piston that can be in open and closed positions.

34. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a chamber with a gas tight o-ring seal.

35. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a gas and liquid tight lid or valve.

36. A method of obtaining a ^{212}Pb solution comprising obtaining a container comprising ^{212}Pb on the walls the and collect the ^{212}Pb in a solution.

ABSTRACT

The present invention relates to assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

Fig. [1] should accompany the abstract.

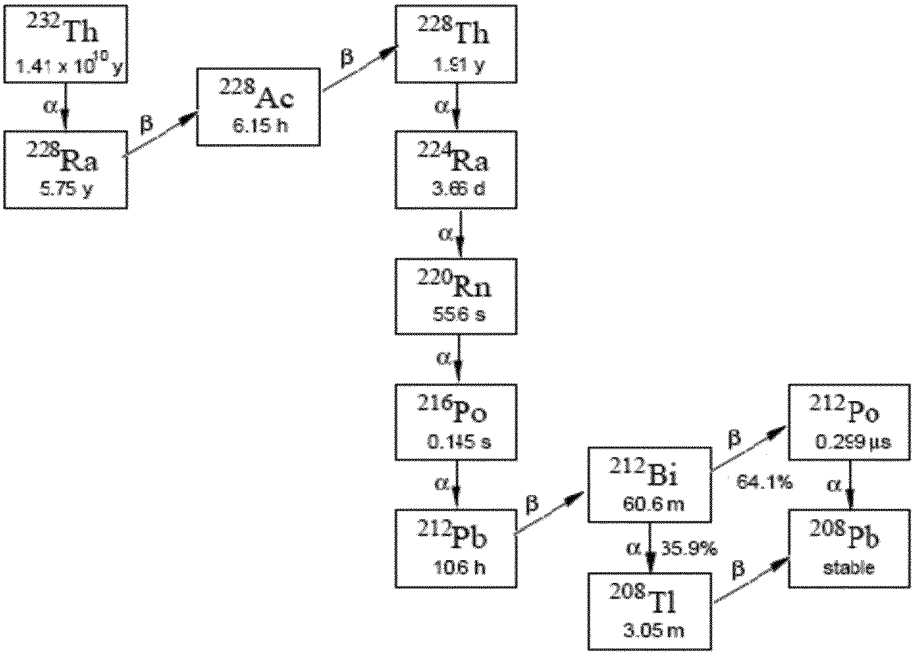

232Th
1.41 x 10^10 y
α
228Ra
5.75 y
β
228Ac
6.15 h
β
228Th
1.91 y
α
224Ra
3.66 d
α
220Rn
55.6 s
α
216Po
0.145 s
α
212Pb
10.6 h
β
212Bi
60.6 m
β
64.1%
212Po
0.299 µs
α
α 35.9%
208Tl
3.05 m
β
208Pb
stable

Fig. 1

Figure 2A

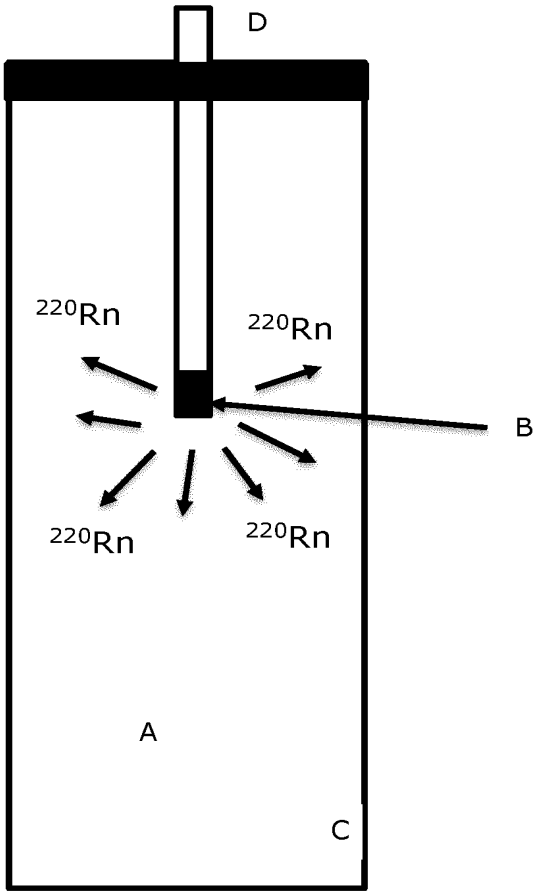


Figure 2B

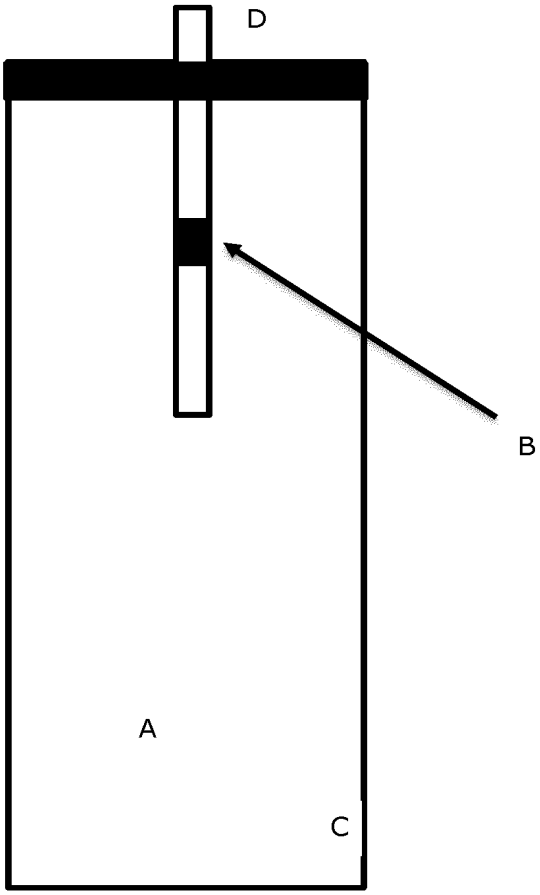


Fig 2

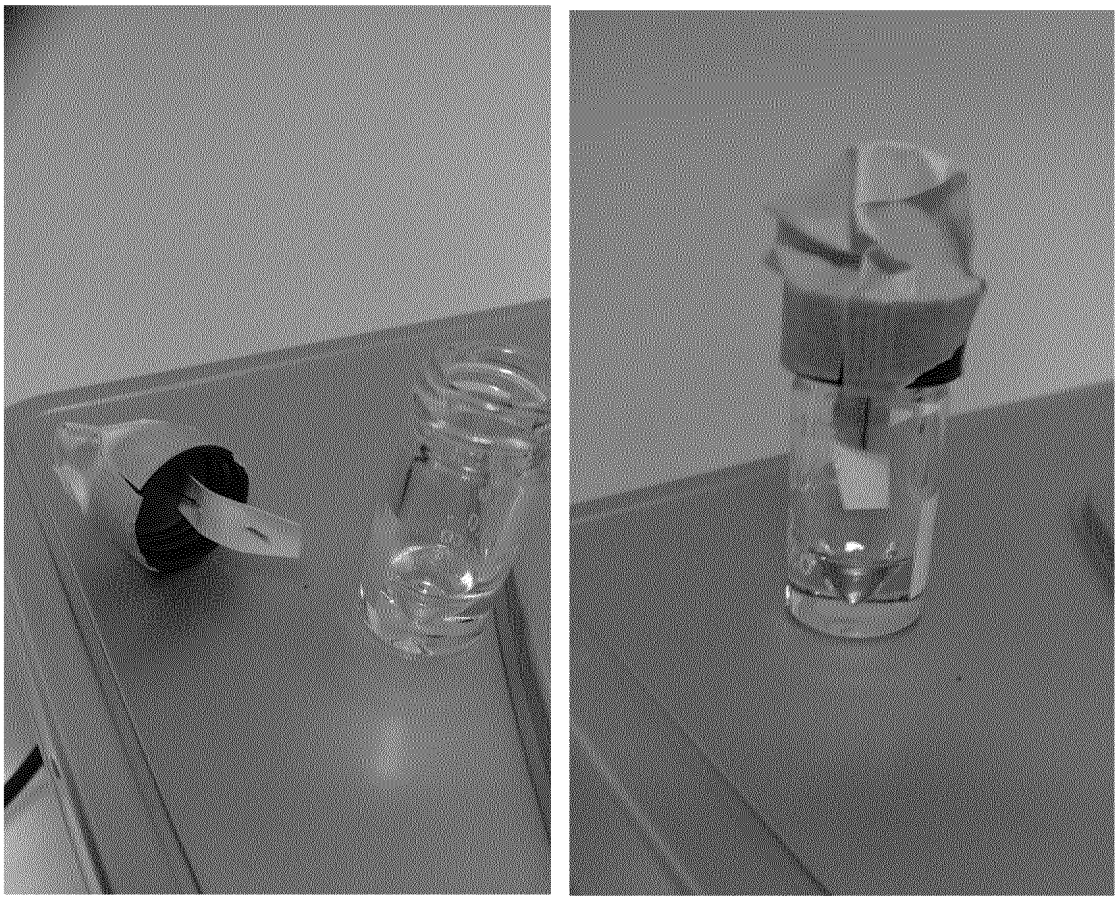


Fig 3

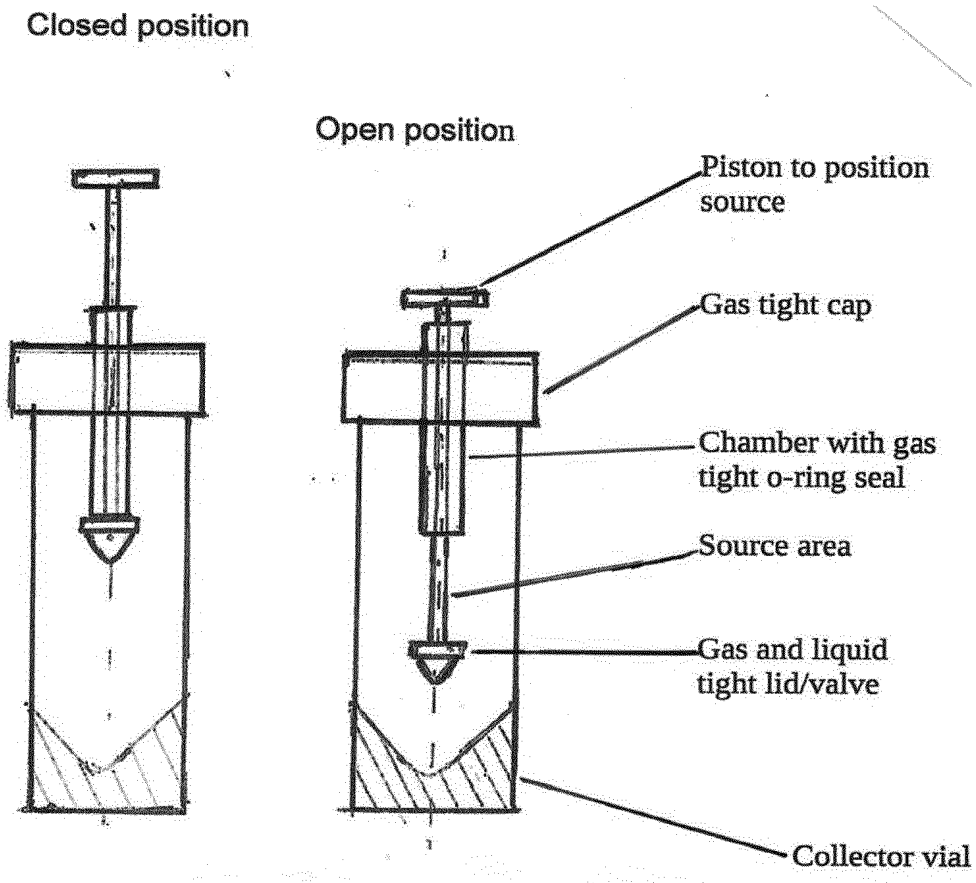
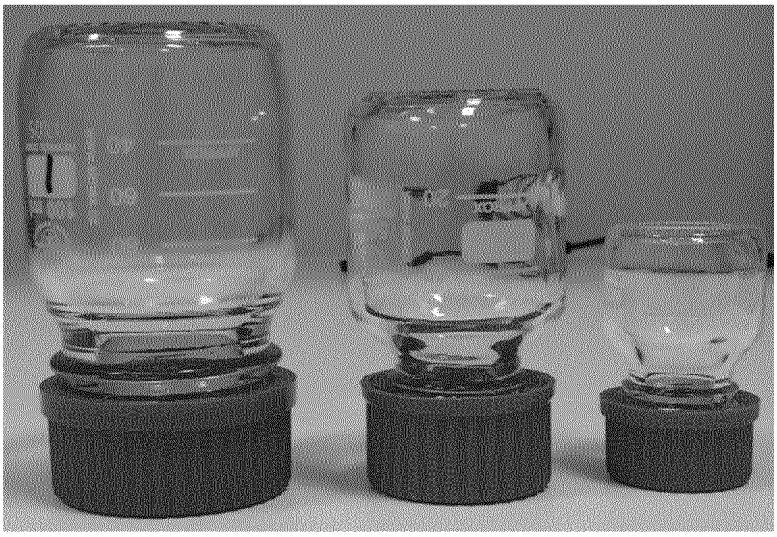

Closed position
Open position
Piston to position source
Gas tight cap
Chamber with gas tight o-ring seal
Source area
Gas and liquid tight lid/valve
Collector vial

Fig 4



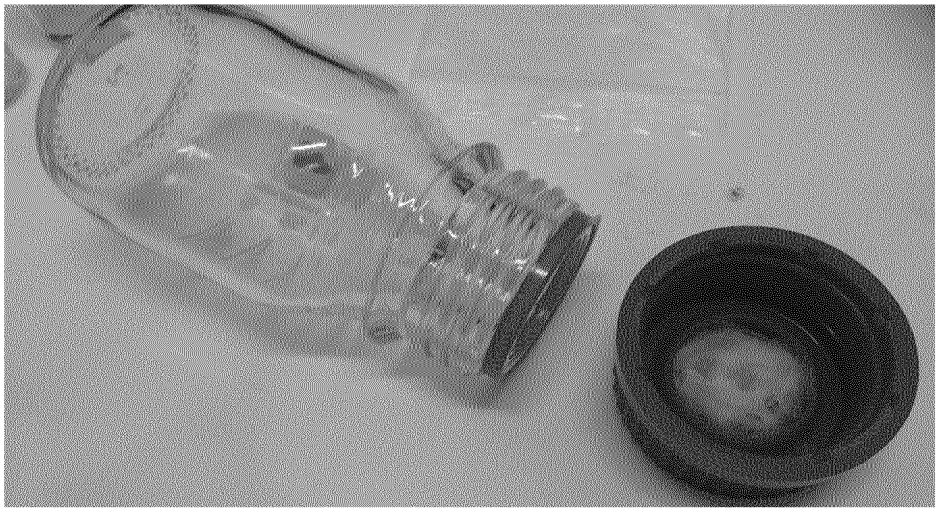


Fig 5

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1. The following indications appeared on record concerning:

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Patentanmeldung Nr.	**Patent application No.**	**Demande de brevet n°**

19213759.4 / EP19213759

The organisation code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP19213759.

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Im Auftrag

For the President of the European Patent Office

Le President de l'Office européen des brevets
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V. Joseph

Anmeldung Nr:
Application no.: 19213759.4
Demande no :

Anmeldetag:
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Anmelder / Applicant(s) / Demandeur(s):

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PRODUCTION OF HIGHLY PURIFIED 212PB

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Am Anmeldetag benannte Vertragstaaten / Contracting States designated at date of filing / Etats contractants désignés lors du dépôt:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Production of highly purified ^{212}Pb

FIELD

The present invention relates to a single chamber diffusion generator (assembly), assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

BACKGROUND

Assemblies for preparing or producing ^{212}Pb have previously been described and based on ^{228}Th bound to stearate in a chamber with another chamber for collecting the ^{212}Pb after ^{220}Rn has diffused from the first chamber (source chamber) to the second chamber (collector chamber).

In another system the $^{228}Th/^{224}Ra$ was extracted from one vessel with a pump generated airflow and $^{220}Rn/^{212}Pb$ collected in another vessel. The system consisted of an “air loop” for transportation of ^{220}Rn and a “fluid loop” for ^{212}Pb rinsing and after rinse collection. This is a quite complex system which is not suitable for shipment and handling, and the potential for leakage or inappropriate use in for example a hospital is significant.

In another system an emanator source is placed inside one chamber and a gas flow passes through and carry ^{220}Rn to another chamber where $^{220}Rn/^{212}Pb$ is collected. After some time, the carrier gas valve is closed, and the collection unit is added a liquid through a top valve and the liquid is collected through a bottom valve. This system is as well relatively complex. Both of these systems need significant work effort of skilled workers and relatively advanced lab equipment and space to operate.

Also, generator systems for ^{212}Pb not relying on ^{220}Rn emanation and diffusion has been presented previously. In one existing generator system ^{224}Ra is bound to ion exchange material and the ^{212}Pb extracted by elution with acid which must be evaporated before it can be used for radiolabeling in another existing system the ^{212}Pb in a solution with ^{224}Ra is used for labelling following the removal of ^{224}Ra by size exclusion purification. Both these methods are working but requires extra time for processing, more so for the first method than the second.

^{212}Pb has a half-life of only 10.6 h. This half-life makes the radioisotope idea for medical applications such as anti-cancer treatment because it acts on its target and without prolonged side effects from a long half-life. However, this feature also makes is difficult to use in a commercial setting involving centralized production and long-distance shipment to end users simply because it decays fast which gives lower yields over time.

Thus, a challenge for the current emanation and diffusion systems is transport distances which can reduce efficiency significantly due to decay of ^{220}Rn before reaching the collection vessels. For example, one system reported a total yield from a 3 days operation of 2.01 MBq ^{212}Pb collected compared from a ^{228}Th source of 7.05 MBq, *i.e.* less than 30% yield. Increasing the operation time did not increase the amount collected and the system was sensitive to the air flow rate.

There is a need for alpha-emitter therapeutics for biomedical applications. Lead-212 (^{212}Pb) is a beta-emitter that decays to short lived progenies producing alpha particles and can thus act as an alpha emitter generator *in vivo* useful in alpha emitter therapeutics.

This industry therefore needs an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

SUMMARY

An object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The described system may be termed a single chamber diffusion generator for ^{212}Pb.

In the following precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb i.e., ^{216}Po, ^{220}Rn, ^{224}Ra etc.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the

second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

In one or more embodiments of the invention the single chamber container assembly is gas tight.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the total amount of radioactivity in the single chamber container assembly is 1 kBq – 100 GBq.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose.

In one or more embodiments of the invention a strip or sphere is attached to the second part, which comprises means for holding the strip or sphere, such as a rod.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap.

In one or more embodiments of the invention the second part comprises a rod that is attached to the means for opening and closing the container.

In one or more embodiments of the invention the means for opening and closing the container is a cap, cover or a lid.

In one or more embodiments of the invention the cap, cover or a lid is made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

In one or more embodiments of the invention the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

In one or more embodiments of the invention the substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is less defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated. The coating may be a film of salt or other suitable material on the inner walls.

In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

DETAILED DESCRIPTION

The present inventors have in response to the need for a simpler, safer system with less size and transport distances to handle the short half-life of ^{220}Rn and ^{212}Pb, designed an assembly whereby the radon producing source is placed inside the collector chamber or container. Instead of using ^{228}Th only as a source is the present invention flexible and can able to use pure ^{224}Ra or a combination of ^{228}Th or ^{224}Ra as source, or even their precursor isotopes.

The assembly of the present inventions can be made very compact and very simple, allowing for a shippable and disposable ^{212}Pb-generator unit. In the present context is assembly, diffusion generator and system are used interchangeably. The described assembly or system may therefore be termed a single chamber diffusion generator for ^{212}Pb.

Thus, an object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the inner walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

An aspect of the invention relates to a method of obtaining a ^{212}Pb solution comprising obtaining the above container comprising ^{212}Pb on the walls and collect the ^{212}Pb in a solution. The ^{212}Pb can be collected in a solution that is in the container before the ^{212}Pb is generated or using a solution that is introduced to the container after the ^{212}Pb has been generated, and then collected. The collection can be done for example using a syringe.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

A huge advantage with the described assembly (or also defined herein as a system or a generator) is the ability to supply ^{212}Pb without the activity level is dictated by the short (10.6 h) half-life of ^{212}Pb. With the described system it is possible to produce a diffusion generator in a centralized production facility and ship it to the end user. A portable disposable generator could be made and shipped to *e.g.* a hospital from one end or the world to the other. For such a disposable unit, a pure ^{224}Ra (without ^{228}Th) is preferable as this would become inactive after 40-50 days approximately avoiding generation of long-lived radioactive waste. Such a diffusion source will steadily produce ^{220}Rn/^{212}Pb in a fashion dictated by the half-life of ^{224}Ra (Table 1 and Figure 1).

^{212}Pb is a member of the thorium natural radionuclide series and can be found in materials containing ^{232}Th ($t_{1/2}$=1.4x10^{10} years). The ^{212}Pb precursor can therefore be chosen based on the intended use. A precursor with longer half-life can be chosen to generate an assembly or system that that will act as a ^{212}Pb generator for continuous production over a longer period of time. Alternatively, an isotope with a shorter half-life be used is the intended use for example is at a hospital or similar where generation of long-lived radioactive waste can be problematic. Naturally a mix of different precursors will therefore also be relevant and also where specific assemblies are needed for the generation of a specific amount of ^{212}Pb over a specific period of time.

Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra. Thus, in the following ^{212}Pb precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb, *i.e.* ^{216}Po, ^{220}Rn, ^{224}Ra ^{228}Th, ^{228}Ac, ^{228}Ra, ^{232}Th.

The decay of these radioisotopes can be seen in figure 1 which clearly indicate the possibility of creating a ^{212}Pb precursor isotope source with different decay profiles and different combinations of precursor isotopes will be able to generate ^{212}Pb at different rates over different periods of time.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb

precursor isotope source is a mixture of ^{228}Th and ^{224}Ra. The source can also be each of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra individually, but due to the decay will a mixture naturally over time occur because ^{232}Th will decay to ^{228}Ra and so on. The key is that the gaseous ^{220}Rn is produced because it will diffuse from the source and later settle on the inner walls of the container as ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

The assembly working as a ^{212}Pb generator unit can be mass produced in a centralized production facility and shipped to end users for application in production of radiopharmaceuticals. It can also be adapted and used for large scale centralized production of ^{212}Pb. Thus, the amount of radioactivity in the assembly can adjusted according to its intended use. In one or more embodiments of the invention will the total amount of radioactivity in the single chamber container assembly therefore be 1 KBq – 100 GBq, such as 1 KBq – 10 MBq, such as 100 KBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq.

The ^{212}Pb precursor isotope source can be in different forms, sizes and shapes depending on the application type. Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$. The ^{212}Pb precursor isotope source can also be in a dry form or in a liquid solution, such as an aqueous solution or a dispersion. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH. The pH can be 1-14, such as pH 1-6, pH 2-6, pH 2-8, pH 4-8, pH 5-7, pH 6-8, pH 7-8, pH 7,2, pH 8-10, pH 8-12, or pH 10-14.

The assembly working as a generator system may be used for preparing single patient dosing or for multiple patient dosing, or even for industrial use. The amount of radioisotope can therefore be adjusted depending on the application of the assembly.

The ^{212}Pb precursor isotope source can be placed on the rod, either directly or on a strip attached to the rod, typically in a very small liquid volume. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid. Such liquid can be in the amount of 1 µl to 1 ml, such as 1 µl to 10 µl, such as 1 µl to 100 µl.

When the container, which can be a vial, can be empty or contain a small volume of liquid in the bottom, that is not touching the source. In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

It is important that the source does not drip or chip of in a fashion that causes cross contamination of the inner surfaces of the collector unit (container) with source material and that the source and source holder can be removed and or withdrawn from the collector without causing cross contamination by contact.

In one or embodiments the source is surrounded by a grid or encapsulated in a porous material to reduce risk of cross-contamination. This encapsulation can be a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

Thus, in one or more embodiments of the invention the container does or does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion. The container may comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source, and the gas permeable barrier impervious to the ^{212}Pb precursor isotope source can be in contact with the ^{212}Pb precursor isotope source. In one or more embodiments of the invention the single chamber container assembly is gas tight.

Figure 2 shows an example of the single chamber container assembly where the container (the first part) is connected with a cap and a rod attached to the cap is used to hold the ^{212}Pb precursor isotope source (the second part) without having this source touch an inner wall of the container during the entire process.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source can therefore be bound to a non-radioactive material, such as particles or a holding material. These can ensure that the source does not contaminate the container. The ^{212}Pb precursor isotope source can be deposited on a strip, sphere or a rod which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers. The strip or sphere can be attached to the second part or be contained or comprised in the second parts, which comprises means for holding the strip or sphere. Such means can for example be a rod.

In one or more embodiments of the invention the second part comprises a rod that is attached to the means for opening and closing the container. The means for opening and closing the container can be a cap, cover or a lid which can be made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose ion exchange resin, natural mineral, polymer.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe. The means for holding can be deposited on a strip or sphere which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers cellulose ion exchange resin, natural mineral, polymer.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap. An alternative design is where the second part is a rubber cap, or septum of another material permeable, and preferential self-sealing, with a syringe tip, with means for holding the ^{212}Pb precursor isotope source attached to the cap or to the inner walls of the container. In this case will user of the assembly be able to dissolve the ^{212}Pb from the inner walls of the container in an aqueous solution though a syringe that is pushed through the cap. The resulting ^{212}Pb in aqueous solution can afterwards be collected by the same syringe which will generate the option of working in a GMP environment which can be directly applied for patient use. Thus, in one embodiment the ^{212}Pb precursor isotope source be withdrawn into a capsule or similar allowing the container to be washed e.g., by using a solution transferred via a syringe through a rubber septum, without having to disassemble the two units. In another embodiment the assembly can be autoclaved, and the solution be of a physiological acceptable composition containing a chelator for disease targeting allowing withdrawal into a syringe and direct infusion with or without the use of a sterile syringe filter. In one embodiment the assembly including all subunits is autoclavable and with a syringe permeable zone on the cap allowing aseptic extraction of ^{212}Pb from the assembly.

After a few hours or days of operation the assembly with the ^{212}Pb precursor isotope source can be used for producing ^{212}Pb by retracting the ^{212}Pb precursor isotope source, e.g., by changing the cap with the attached ^{212}Pb precursor isotope source to a new cap without radioactivity and washing the inner surface with a suitable solution to dissolve surface deposited ^{212}Pb and progenies. Since the ^{212}Pb solution is free from long lived predecessor radionuclides it can be used directly without further chemical processing to label carrier molecules for e.g. cancer therapy.

The ^{212}Pb precursor isotope source can associated with a needle, rod or a strip of a material of which ^{212}Pb precursor isotope source is attached to allow diffusion of ^{220}Rn. The source may or may not contain a holder for the radioactive part and a grid or ring or similar surrounding the source to prevent cross contamination when the ^{212}Pb precursor isotope source is withdrawn from the container. In one embodiment it may be attached to a screw cap that can be used to close the container. The ^{212}Pb precursor isotope source can be isolated from the container by withdrawing the source into a cover. This will ensure that the source does not cross contaminate the inner walls of the container while the ^{212}Pb is extracted, and also limit risk of exposure to the user of the assembly. It is important that after a period of decay the ^{212}Pb precursor isotope source and the ^{212}Pb adsorbed onto the vial inner surfaces can be separated by withdrawing the ^{212}Pb precursor isotope source form the container, e.g. by replacing the screw cap of which the source is attached

by a rod or similar with a standard gas tight screw cap. Thus, In one special embodiment is the ^{212}Pb precursor isotope source equipped with a retractable radioactive source that is withdrawn into the cap similar to a "click pen system" or similar for isolating the source from the generator units interior surfaces and thus not require the disassembling and replacement of the cap (e.g. Figures 2 and 4). Thus, the second part of the assembly can comprise a piston that can be in open and closed positions. The second part of the assembly can also comprise a chamber with a gas tight o-ring seal. In one or more further embodiments the assembly comprises a gas and liquid tight lid or valve in the second part.

The second part of the assembly can comprise a needle, rod or strip which may be supplied with a small ball of a material that can absorb radium or thorium including glass wool, quartz wool, paper, cotton, stearate or another fatty acid, metal, cellulose, natural mineral, polymer, ion exchange resin, or other fibrous material. The composition of the holder of the precursor isotope should be chosen with care according to the known affinity of radon for various materials. A material that ^{228}Th and or ^{224}Ra has a good adsorption or absorption to and ^{220}Rn has a low affinity for would be suitable. The container can be made of a glass (including quartz), polymer and or metal, such as a glass vial, with a screw cap or similar, whereby the source is attached to the screw cap.

The container can have a volume of 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml. The volume will depend on the use, where single use generally will be smaller and industrial batch containers will be larger.

Minimizing risk of cross contamination is important and the assembly has to be designed so that the ^{212}Pb precursor isotope source does not come into contact with the inner walls of the container. Thus, in one or more embodiments of the invention the container is substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The definition of substantially free depends on use of the ^{212}Pb produced in the assembly. In one or more embodiments of the invention is "substantially free" defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb.

The container is surrounding, but not touching, the ^{212}Pb precursor isotope source. This should be made of an appropriate material, for example glass, plexiglass, metal, ceramics, polymer including polypropylene and Teflon or other materials suitable for allowing deposition of ^{220}Rn and/or ^{212}Pb on its inner walls and allowing ^{212}Pb to be dissolved when washed with a suitable solution for further use in radiolabeling. A solution can be used to wash the inner walls of the container to extract radionuclides, mainly ^{212}Pb and progenies. It may be present during the ^{212}Pb production period in the assembly or be applied after the ^{212}Pb precursor isotope source has been removed or withdrawn. In one embodiment the solution and an acidic or alkaline solution that can be

transferred and neutralized before use for administration to a patient. In one embodiment the solution may be water of a suitable purity for pharmaceutical use. Solution volume of 1 ul to 1 liter for single dosing, e.g. 100 ul to 10 ml, and 1 ul to 10 liter or higher for multiple dosing may be used.

The container may or may not contain a surface film on the inner surfaces or some liquid to assist in collecting the diffusion product. This surface film can for example be a coating. Size and volume may be in microliter to ml for single dosing units and in microliters to tens of liters or higher for multiple dosing. The inner walls of the container can be coated. This coating can ensure that ^{212}Pb settles in an optimal way. In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb. It is also possible that the inner walls are coated with one or more compounds where a complex with ^{212}Pb is needed. In one or more embodiments of the invention the inner walls of the container are coated with a chelator which is TCMC or a variant hereof. The coating may be a film of salt or other suitable material on the inner walls.

In a special embodiment the container is washed directly with the reaction solution containing the complexing agent to yield a radiolabeling solution which after a suitable reaction time can be used directly for therapeutic purposes. In one embodiment the final product solution is autoclaved and or sterile filtered before administration to a subject in need thereof.

In one embodiment the assembly can be attached to a flushing and filtering circuit whereby when the source is retraced from the chamber a reservoir of a solution is connected and an outlet with a sterile filter and a syringe or vacuum pump is attached to flush the chamber and collect the flushing solution, *e.g.*, in similar fashion as for ^{99m}Tc-generators.

In general, surface ratios between precursor source holder and the collector chamber inner surfaces should be optimized so that as much as possible of the generated ^{212}Pb settles on the collector chamber surfaces. The surfaces may be smooth, or porous or may contain structures to increase surface area relative to the diffusion subunit, container or assembly.

The production can be a production period of 5 hours, 10, hours, 20 hours or more. Afterwards the source may be withdrawn from the chamber into a tube-shaped holder or similar with a gas and liquid tight lid in the bottom that closes when the source is completely withdrawn. This allows for addition of a washing solution, *e.g.*, by a syringe, or activation of a flushing and collecting circuit *e.g.* similar to that of a ^{99m}Tc generator.

In a special embodiment the single chamber diffusion unit has its ^{212}Pb precursor isotope source as a film on the inside surfaces of the assembly and has the ^{212}Pb collector unit (container) inserted into the source covered surfaces without touching these, *i.e.* a reverse configuration compared to what is shown in figure 2.

In another embodiment the diffusion generator is subject to temperature manipulation, either elevated or reduced temperature vs 20 oC.

The use of the invention for includes in the production of radiopharmaceuticals, medical devices and or standardization sources for ^{212}Pb. The assembly of the present invention can be used to generate a ^{212}Pb standard for calibrations.

In one or more embodiments of the invention is the assembly of the present invention comprised in kit with the ^{212}Pb precursor isotope source, and a solution containing a chelator, and a compound that for use in therapy. Such compound can be a nano- or microparticle. In one embodiment such a kit will contain a ^{212}Pb precursor isotope source, a solution for washing the inner walls of the container and a solution or dry form of a carrier compound, for example a chelator, micro- or nanoparticles.

Tables

Table 1. Main radiation properties of the ^{224}Ra series.

Radionuclide (half-life)	Alphas and betas (mean energy in MeV)	X-rays and gammas Energy and % abundance
^{224}Ra (3.6 days)	α 5.6	241 keV, 4.1%
^{220}Rn (55.6 s)	α 6.3	
^{216}Po (145 ms)	α 6.8	
^{212}Pb (10.6 h)	β 0.1	75 keV, 10.3% 77 keV, 17.1% 87 keV, 6.0% 90 keV, 1.5% 239 keV, 43.6% 300 keV, 3.3%
^{212}Bi (10.6 h)	α 6.1 × 0.36 (2.2 MeV effective[1]) β 0.7 × 0.64 (0.4 MeV effective)	727 keV, 6.7% (4.3% effective)
^{212}Po (299 ns) (64% branch)	α 8.8 (5.6 effective)	
^{208}Tl (3.1 min) (36% branch)	β 0.6 (0.2 MeV effective)	75 keV, 3.4% (1.2% effective) 511 keV, 22.6% (8.1% effective) 583 keV, 85.0% (30.6% effective) 860 keV, 12.5% (4.5% effective) 2615 keV, 99.8% (35.9% effective)

[1]Average per ^{224}Ra transformation due to branching. Only X-rays or gammas above 1% effective abundance accounted for. Adds up to a total effective energy of approximately 26.5 MeV of alpha of 0.7 MeV of beta per complete decay of a ^{224}Ra atom via progenies to a stable ^{208}Pb atom.

Table 2. A pure ^{212}Pb source with initial 100 MBq ^{212}Pb kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h

^{212}Pb (MBq) total	23.1	4.4	0.92	0.192

Table 3. Lead-212 production from a source with initial 100 MBq ^{224}Ra kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	72.9	63.4	53.1
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	51.0	44.4	37.2

Table 4. Lead-212 production from a source with initial 100 MBq ^{224}Ra source emptied for ^{212}Pb every 24 h.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	58.2	48.1	39.8
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	40.7	33.7	27.9

The following figures and examples are provided below to illustrate the present invention. They are intended to be illustrative and are not to be construed as limiting in any way.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the decay of ^{232}Th to its progenies. The decay type (alpha or beta) is indicated and so is the half-lives. These half-lives are important because they dictate the decay rate and are therefore also key in deciding the optimal mix of isotopes as ^{212}Pb precursor isotope source for the production of ^{212}Pb.

Figure 2A shows a figure of the single chamber container assembly with the container (A), the a ^{212}Pb precursor isotope source (B) that generates the ^{220}Rn gas which is released into the single chamber container assembly and after decay settled as ^{212}Pb onto the inner walls of the container (C). The upper part of the single chamber container assembly (D) is the second part which comprises the ^{212}Pb precursor isotope source and in this case a cover/cap with a rod attached pointing towards the centre of the container thus enabling ^{212}Pb precursor isotope source release of ^{220}Rn into the container. Figure 2B shows a situation where the ^{212}Pb precursor isotope source (B) has been withdrawn into a gas tight seal that ensures that no ^{220}Rn is released into the container. The ^{212}Pb precursor isotope source can also be removed entirely from the assembly.

Figure 3 shows picture of a crude version of the generator system based on a 3 ml v-vial with an membrane inserted open top screw cap penetrated by a syringe tip (with position fixed by tape on top of screw cap) and with a strip of laboratory bench paper attached to the syringe tip (left picture shows the ^{212}Pb precursor isotope source and container). The ^{212}Pb precursor isotope source is placed onto the strip by a pipette before the screwcap with the source is carefully attached to the vial (right picture). It is very important that the source is not touching the vial when assembling and disassembling the unit to avoid cross-contamination.

Figure 4. An example of a single chamber diffusion generator for ^{212}Pb with a retractable source simplifying washout of ^{212}Pb from the inner surfaces by having syringe permeable zones on the lid supplied with septum, a syringe could be used for washing of the interior surfaces without radionuclide cross contamination when the unit is put in closed position.

EXAMPLES

Example 1 - Calculation of the relative ^{212}Pb daughter nuclide level at various time points

Background. The development and use of pure ^{212}Pb in therapeutic radiopharmaceuticals is hampered by the short half-life (10.6 h) of the radionuclide making it almost impossible to produce a product in a centralized fashion and shipped to the end user. If ^{224}Ra is used as a short-term generator for ^{212}Pb the level of ^{212}Pb activity can be maintained essentially according to the half-life of ^{224}Ra, which is 3.6 days. The variation in ^{212}Pb level in a sealed source of pure ^{224}Ra is shown.

Method: The ingrowth of ^{212}Pb from a pure ^{224}Ra source were calculated using a universal activity calculator.

Results: Table 2 shows the amount of ^{212}Pb at various time points after the production of a pure ^{224}Ra pharmaceutical solution and storage in a gas tight container. As can be seen the pure ^{212}Pb source rapidly decays and lose more than 75% per 24 h. Table 3 shows the amount of ^{212}Pb present in a sealed source of ^{224}Ra at the same time points. As can be seen the ^{212}Pb activity is maintained at a high level (> 50%) at least up to 96 h.

Table 4 shows the effect of "milking" a ^{224}Ra precursor-based generator for ^{212}Pb several times during a 96-h period. Notice that the total combined output of ^{212}Pb can exceed the source radioactivity by more than a factor of 1.5 when ^{212}Pb is removed once a day for up to 4 days.

The data also shows that significant amount of daughter nuclide is present within a relatively short time frame when starting with pure ^{224}Ra. It is noteworthy though that the ratio of ^{212}Pb to ^{224}Ra in the solution reaches 1 after 36 hours and thereafter gradually increases to about 1.1 of which is kept for the rest of the time until complete decay. In conclusion, using ^{224}Ra as a source for ^{212}Pb makes the logistic of centralized production and shipment to end users possible providing an easy way to extract the ^{212}Pb from ^{224}Ra exist.

Example 2 - Preparation of radionuclides and counting of radioactive samples

In the following, all work with the concentrated radioactive preparations including evaporation of solvent etc was performed in a glove-box. A source of ^{228}Th in 1 M HNO3 was acquired from a commercial supplier. Ac-resin was obtained from Eichrom Technologies LLC (Lisle, IL, USA) in the form of a pre-packed cartridge.

Radium-224 was made from ^{228}Th bound to Actinide resin (Eichrom Technologies, LLC) by eluting a column containing actinide resin with immobilized ^{228}Th with 1 M HCl. The eluate was purified on a second Ac-resin column and the eluate evaporated to dryness using an evaporation vial with a

cap with gas inlet and outlet placed in a heater block at approximately 110 ◦C and a gentle stream of nitrogen gas to evaporate of the solvent. When the evaporation vial was empty from solvent it was added 0.1 M HCl to dissolve the residue, typically 200-400 µl. Typically, more than 70% of the ^{224}Ra present in the ^{228}Th source could be extracted and purified using the described methods.

Radioactive samples were counted on a Cobra II Autogamma counter (Packard Instruments, Downer Grove, IL, USA). During extraction of ^{224}Ra from the ^{228}Th source, a CRC-25R dose calibrator (Capintec Inc., Ramsey, NJ, USA) was used.

Example 3 - Determining net count rate for ^{212}Pb in a ^{212}Pb/^{224}Ra mixture before radioactive equilibrium has been reached

After more than 3 days, i.e., “equilibrium” a sample will for practical purposes have 1.1 times ^{212}Pb vs ^{224}Ra.

Regardless of whether ^{212}Pb is higher or lower than equilibrium it can be assumed that this is reached after 3 days since surplus ^{212}Pb is reduced by 99% and the ingrowth of ^{212}Pb from ^{224}Ra is practically complete vs. “equilibrium”.

Using the Cobra II Autogamma counter with a counting window setting from 70-80 KeV gives mainly the ^{212}Pb with very little contribution from other radionuclides in the ^{224}Ra series. Radium-224 must be indirectly counted when the initial ^{212}Pb has vanished and equilibrium between ^{224}Ra and ^{212}Pb has been reached (after approximately 3 days). This indirect counting requires the sample to be stored in a relatively gas tight containers as otherwise the ^{220}Rn may escape preventing the radionuclide equilibrium of 1.1 between ^{212}Pb and ^{224}Ra to be reached.

Since sampling and counting may be separated by some time, the net count rate for ^{212}Pb can be adjusted for decay to determine the net ^{212}Pb count rate at the time of sampling. By storing ^{212}Pb samples for a week or longer and remeasure, the amount of ^{224}Ra contaminant can be determined as activity after about 110 hours of storage would not be ^{212}Pb but must be from longer lived precursor isotope.

Example 4 - A simplified single chamber (diffusion chamber generator) assembly for ^{212}Pb production (Figure 3).

A 3 ml v-vial with an open top cap. The open top cap was supplied with a membrane permeable by a syringe tip. A syringe tip was pushed through the membrane and fixed with tape on top to lock the position of the tip with regard to the open top cap. On the syringe tip vas placed a strip of absorbent paper about 0.5 X 3 cm by inserting the syringe tip in two holes in the strip. The paper

strip was added 2-40 ul ^{224}Ra solution. Thereafter the cap was placed carefully onto the v-vial while the syringe tip and radioactive strip were not to touch the inside of the v-vial. Thereafter the assembly was standing for various time to produce ^{212}Pb via ^{220}Rn diffusion from the strip to the space surrounding the strip. The ^{212}Pb tended to settle on the inner surfaces of the v-vial. Depending on the liquid volumes used for applying the ^{224}Ra source onto the strip, there may be some condensation of liquid due to evaporation/condensation of the liquid applied. Alternatively, the source could be dried before assembling the unit to avoid any solvent condensation on the v-vial inner surfaces.

Example 5A: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a paper strip.

Methods: The assembly was assembled with ^{224}Ra placed on the strip of the diffusion subunit inserted in a v-vial according to Figure 3, and was standing for 17.5 h or more to produce ^{220}Rn and ^{212}Pb. Production of ^{212}Pb evaluation of radiochemical purity of product. At the end of the production period the whole unit was measured on a Capintec dose calibrator. The product was evaluated by separating the source from the container and cap the latter with a gas tight screw cap and measure immediately in the Capintec dose calibrator. The purity of the product was determined by measuring the collector subunit again after a few days when all the ^{212}Pb had decayed but the presence of longer-lived predecessor nuclides ^{224}Ra and ^{228}Th would have been measurable. Results: Highly purified ^{212}Pb was collected in the collector subunit with a relevant yield of 65.6% (range 62.7-69.9% n=4) and with no measurable longer-lived precursor nuclides present (< 0.5%). In conclusion: The assembly was effective in producing and collecting purified ^{212}Pb in an easy manner without need for further purification.

Example 5B: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a parafilm strip. The experiment from 5A was repeated except that a parafilm strip was used instead of paper a strip to carry the precursor isotope source.

Results: The yield of ^{212}Pb on the inner surfaces of the collector subunit (vial or container) was found to be only 19.3%. In contrast a unit with paper strip run in parallel with exact same configuration and emanation period gave a yield of 63.9%. In conclusion, the material used for absorbing and holding the ^{212}Pb precursor isotope source could greatly affect the yield of ^{212}Pb on the collector subunit or container.

Example 6: Dissolving of ^{212}Pb from the container using a solution.

Methods: The collector vial was added 0.3-0.5 ml 0.1 M HCl which was gently swirled to contact the inner surfaces with the liquid and counted in the Capintec dose calibrator. Thereafter the liquid was transferred to an Eppendorf tube and measured in the Capitec dose calibrator. The extraction yield was 740 % (range 70.0-76.9%, n=3) when the collector subunit (3 ml v-vial), was washed one single time with 0.3 ml 0.1 M HCl. In conclusion, ^{212}Pb absorbed onto the surfaces of the container was rapidly and with good yield dissolved by a solution useful for radiopharmaceutical processing.

Example 7: Thin layer chromatography analyses

Thin layer chromatography (TLC) was performed using chromatography strips (model # 150-772, Biodex Medical Systems Inc, Shirley, NY, USA). A small beaker with about 0.5 ml of 0.9% NaCl was used to place strips with a sample spot in. To the strip was typically added 1-4 µl of sample at approximately 10% above the bottom of the strip. After the solvent front had moved to about 20% from the top of the strip, the strip was cut in half and each half was placed in a 5 ml test tube for counting. In this system radiolabeled antibody and free radionuclide does not migrate from the bottom half while radionuclide complexed with EDTA migrates to the upper half. A formulation buffer (FB) consisting of 7.5% human serum albumin and 1 mM EDTA in DPBS and adjusted to approximately pH 7 with NaOH was mixed with the radioconjugates in ratio 2:1 for at least 5 minutes before application to the strips to determine free radionuclide. It was verified that in a test solution with free ^{212}Pb was the radionuclide was completely (> 99%) complexed by the EDTA, when mixed with FB, and would travel to the upper half of the TLC strip.

Example 8: In situ chelation of ^{212}Pb in solutions.

Background: The labeling properties of the ^{212}Pb extracted with 0.1 M HCl from the containers was evaluated. Methods: A 10:1 ratio of ^{212}Pb in 0.1 M HCl and 5 M ammonium acetate was used before addition of the chelators, resulting in a pH range of 5 – 6 for the reactions. Reaction times of 15-30 minutes at 37 °C, were tested. For PSMA-617 solutions of 5 ug per 100 ul was labeled with good yield of 96.6% as determined by TLC. Also, TCMC-conjugated Herceptin antibody solution of approximately 1.0 mg/ml was labeled with pure ^{212}Pb with a good yield of 98.9%. In conclusion: Lead-212 produced with the assembly was readily complexed with small molecular and large molecular conjugates indicating suitability for use in production of ^{212}Pb based radiopharmaceuticals.

Example 9 - Production of ^{212}Pb from the ^{224}Ra source when unit is kept sealed and emptied only at one time point

Table 3, lower row, shows the example of an output from a diffusion generator emptied after various time points after insertion of the source of 100 MBq of ^{224}Ra into the unit. As shown the generator gives a relatively stable output of ^{212}Pb for up to 96 h.

Example 10 - Production of ^{212}Pb from the ^{224}Ra source when unit is emptied once a day for four days e.g. if used for fractionated radionuclide therapy etc.

Table 4 shows the output when the assembly is "milked" once every 24 h. The combined output is a total of 151.5 MBq of ^{212}Pb when starting with a 100 MBq source. In conclusion, the one chamber assembly is suitable for single dose as well as fractionated dose production.

Example 11 - Example of an assembly with a retractable source (Figure 2 and Figure 4)

The materials used may be of glass (including quartz), polymer, metal, ceramic or other suitable materials for pharmaceutical containers. The rod in figure 2 (piston in figure 4) slides in a tube with o rings or similar at the top to secure gas tight seal. The valve at the bottom of the rod is gas and liquid tight in the closed position for the unit.

In the open position the source will be exposed inside the container and emanate ^{220}Rn and cause deposit of ^{212}Pb onto the inner surface. In closed position the source is sealed off from the container (Figure 2B) and the container surfaces can be contacted with a suitable solution to dissolve ^{212}Pb.

In one embodiment where the cap has syringe permeable membrane, a sterile syringe with a sterile solution is used to extract the ^{212}Pb without removing the cap. When such unit has been autoclaved before the extraction of ^{212}Pb, the complete procedure can be performed in an aseptic/sterile fashion.

CLAIMS

1. A method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of:

- providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source,
- connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided,
- allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly,
- removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and
- obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

2. An assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

3. A single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

4. The method according to claim 1, the assembly according to claims 2-3, wherein the single chamber container assembly is gas tight.

5. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

6. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

7. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

8. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

9. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

10. The method and the assembly according to any one of the proceeding claims, wherein the total amount of radioactivity in the single chamber container assembly is 1 KBq – 100 GBq.

11. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

12. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

13. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

14. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

15. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid.

16. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a strip or sphere which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers.

17. The method and the assembly according to claims 15-16, wherein a strip or sphere is attached to the second part, which comprises means for holding the strip or sphere, such as a rod.

18. The method and the assembly according to claim 17, wherein the second part comprises a syringe, or wherein the rod is the syringe.

19. The method and the assembly according to claim 18, wherein the syringe tip has been pushed through a rubber cap.

20. The method and the assembly according to any one of the proceeding claims, wherein the second part comprises a rod that is attached to the means for opening and closing the container.

21. The method and the assembly according to claim 20, wherein the means for opening and closing the container is a cap, cover or a lid.

22. The method and the assembly according to claim 21, wherein the cap, cover or a lid is made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

23. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

24. The method and the assembly according to any one of the proceeding claims, wherein the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

25. The method and the assembly according to claim 24, wherein the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

26. The method and the assembly according to claims 1-23, wherein the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

27. The method and the assembly according to any one of the proceeding claims, wherein volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

28. The method and the assembly according to any one of the proceeding claims, wherein substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is less defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % relative radioactivity.

29. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated.

30. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

31. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

32. The method and the assembly according to any one of the proceeding claims, wherein the container comprises an aqueous or an oil solution.

33. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a piston that can be in open and closed positions.

34. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a chamber with a gas tight o-ring seal.

35. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a gas and liquid tight lid or valve.

36. A method of obtaining a ^{212}Pb solution comprising obtaining a container comprising ^{212}Pb on the walls the and collect the ^{212}Pb in a solution.

ABSTRACT

The present invention relates to assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

Fig. [1] should accompany the abstract.

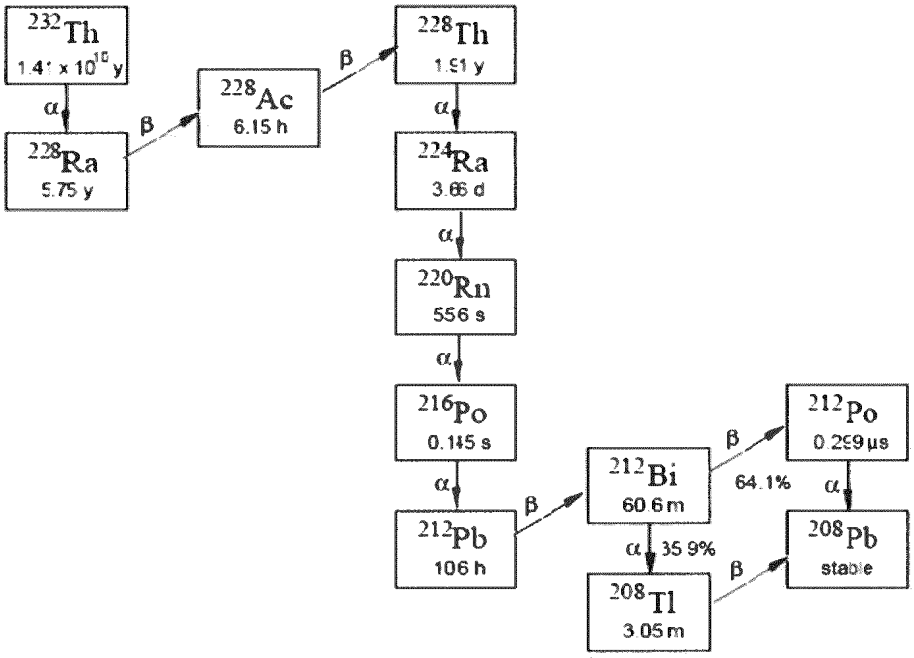

232Th
1.41 x 10^10 y
α
228Ra
5.75 y
β
228Ac
6.15 h
β
228Th
1.91 y
α
224Ra
3.66 d
α
220Rn
55.6 s
α
216Po
0.145 s
α
212Pb
10.6 h
β
212Bi
60.6 m
β
64.1%
212Po
0.299 µs
α
α
35.9%
208Pb
stable
β
208Tl
3.05 m

Fig. 1

Figure 2A

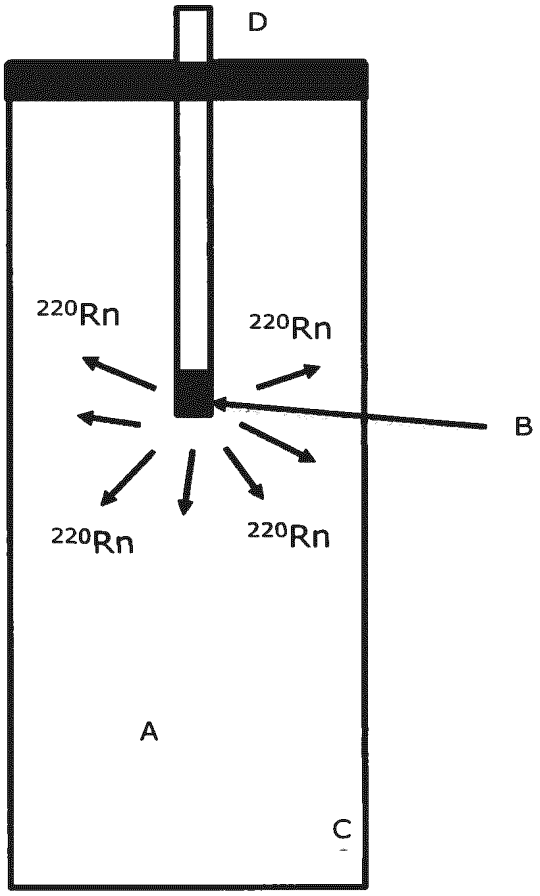


Figure 2B

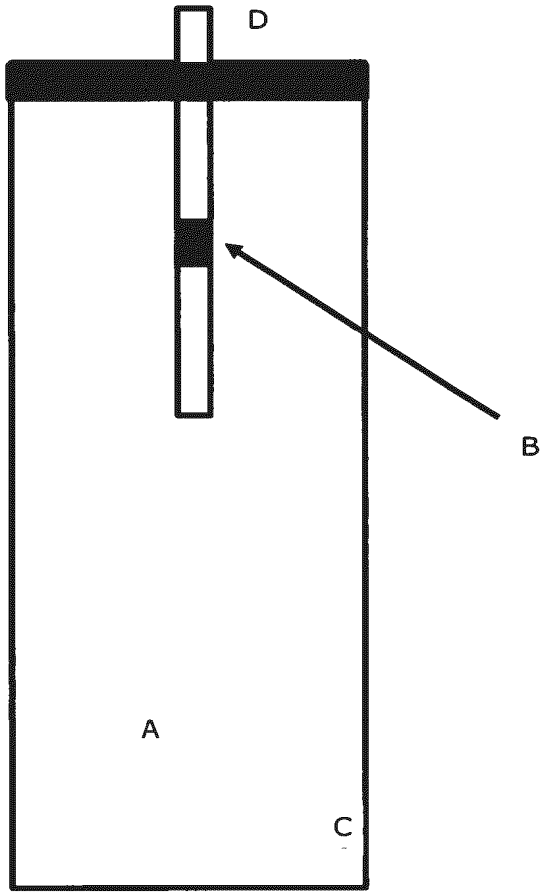


Fig 2

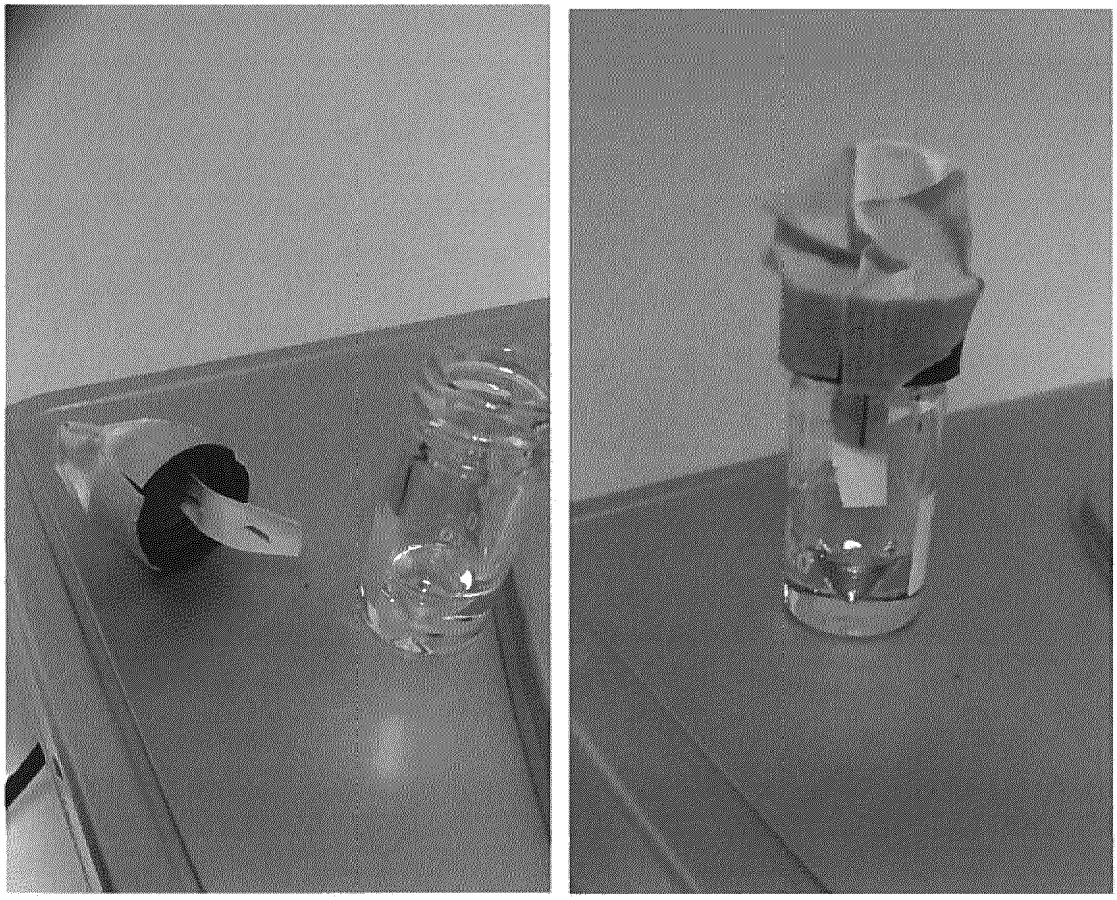


Fig 3

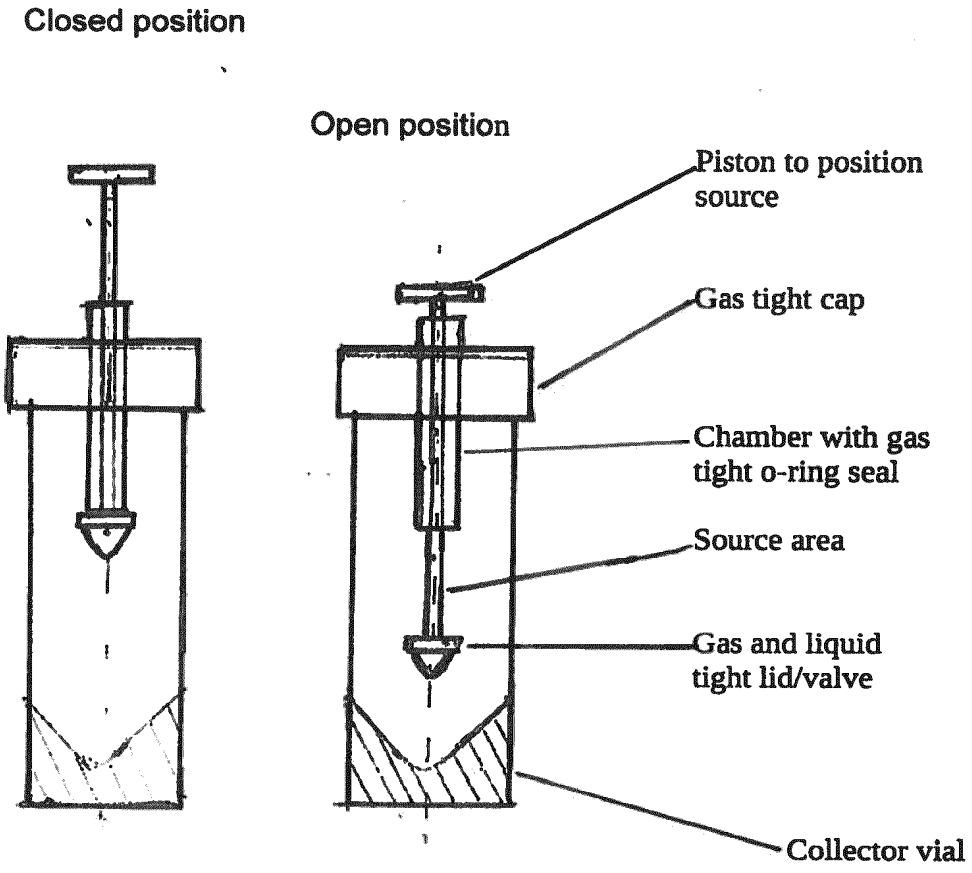

Closed position
Open position
Piston to position source
Gas tight cap
Chamber with gas tight o-ring seal
Source area
Gas and liquid tight lid/valve
Collector vial

Fig 4

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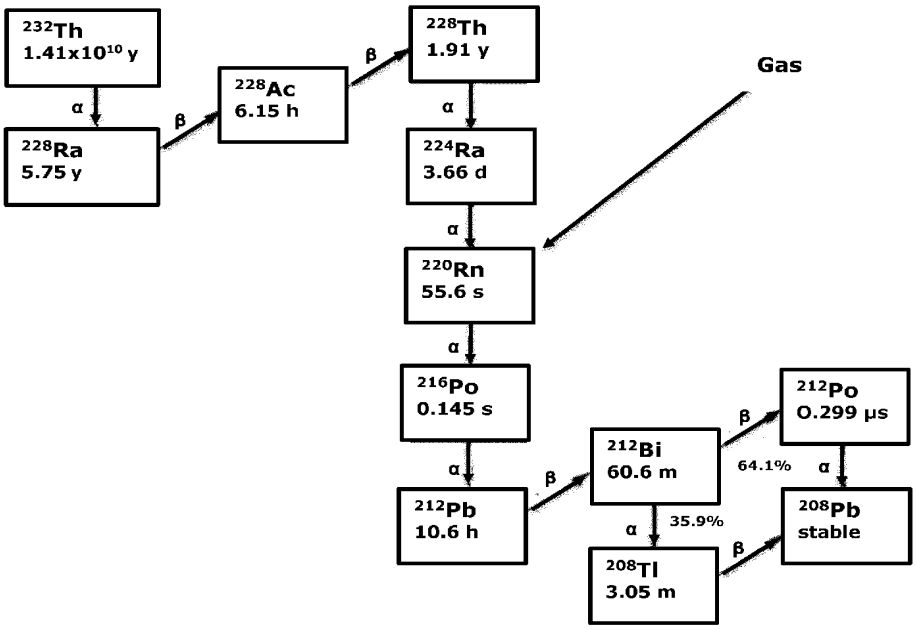
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(54) Title: PRODUCTION OF HIGHLY PURIFIED 212PB



(57) Abstract: The present invention relates to assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

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Production of highly purified ^{212}Pb

FIELD

The present invention relates to a single chamber diffusion generator (assembly), assemblies and method for obtaining a container comprising ^{212}Pb on the walls obtained from a ^{212}Pb precursor isotope source. The invention provides an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

BACKGROUND

Assemblies for preparing or producing ^{212}Pb have previously been described and based on ^{228}Th bound to stearate in a chamber with another chamber for collecting the ^{212}Pb after ^{220}Rn has diffused from the first chamber (source chamber) to the second chamber (collector chamber).

In another system the $^{228}Th/^{224}Ra$ was extracted from one vessel with a pump generated airflow and $^{220}Rn/^{212}Pb$ collected in another vessel. The system consisted of an “air loop” for transportation of ^{220}Rn and a “fluid loop” for ^{212}Pb rinsing and after rinse collection. This is a quite complex system which is not suitable for shipment and handling, and the potential for leakage or inappropriate use in for example a hospital is significant.

In another system an emanator source is placed inside one chamber and a gas flow passes through and carry ^{220}Rn to another chamber where $^{220}Rn/^{212}Pb$ is collected. After some time, the carrier gas valve is closed, and the collection unit is added a liquid through a top valve and the liquid is collected through a bottom valve. This system is as well relatively complex. Both of these systems need significant work effort of skilled workers and relatively advanced lab equipment and space to operate.

Also, generator systems for ^{212}Pb not relying on ^{220}Rn emanation and diffusion has been presented previously. In one existing generator system ^{224}Ra is bound to ion exchange material and the ^{212}Pb extracted by elution with acid which must be evaporated before it can be used for radiolabeling in another existing system the ^{212}Pb in a solution with ^{224}Ra is used for labelling following the removal of ^{224}Ra by size exclusion purification. Both these methods are working but requires extra time for processing, more so for the first method than the second.

^{212}Pb has a half-life of only 10.6 h. This half-life makes the radioisotope idea for medical applications such as anti-cancer treatment because it acts on its target and without prolonged side effects from a long half-life. However, this feature also makes is difficult to use in a commercial setting involving centralized production and long-distance shipment to end users simply because it decays fast which gives lower yields over time.

Thus a challenge for the current emanation and diffusion systems is transport distances which can reduce efficiency significantly due to decay of ^{220}Rn before reaching the collection vessels. For example, one system reported a total yield from a 3 days operation of 2.01 MBq ^{212}Pb collected compared from a ^{228}Th source of 7.05 MBq, *i.e.* less than 30% yield. Increasing the operation time did not increase the amount collected and the system was sensitive to the air flow rate.

There is a need for alpha-emitter therapeutics for biomedical applications. Lead-212 (^{212}Pb) is a beta-emitter that decays to short lived progenies producing alpha particles and can thus act as an alpha emitter generator *in vivo* useful in alpha emitter therapeutics.

This industry therefore needs an improved system and method for producing ^{212}Pb in high purity without the need for processing, with high yields, and which safely and efficiently can be transported to the locations where it is to be used.

SUMMARY

An object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The described system may be termed a single chamber diffusion generator for ^{212}Pb.

In the following, precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb i.e., ^{216}Po, ^{220}Rn, ^{224}Ra etc.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the

second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

In one or more embodiments of the invention the single chamber container assembly is gas tight.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th.The ^{212}Pb activity may vary from typically 0% to 114% of the ^{224}Ra precursor activity in the generator depending on the ingrowth status. The ^{212}Pb activity can be at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % of the ^{224}Ra precursor activity.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the total amount of radioactivity in the single chamber container assembly is 1 kBq – 100 GBq.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose.

In one or more embodiments of the invention a strip or sphere is attached to the second part, which comprises means for holding the strip or sphere, such as a rod.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap.

In one or more embodiments of the invention the second part comprises a rod that is attached to the means for opening and closing the container.

In one or more embodiments of the invention the means for opening and closing the container is a cap, cover or a lid.

In one or more embodiments of the invention the cap, cover or a lid is made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

In one or more embodiments of the invention the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

In one or more embodiments of the invention the substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is less defined as less than 3 % ^{224}Ra of the ^{212}Pb

precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated. The coating may be a film of salt or other suitable material on the inner walls.

In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

In one or more embodiments of the invention the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

DETAILED DESCRIPTION

The present inventors have in response to the need for a simpler, safer system with less size and transport distances to handle the short half-life of ^{220}Rn and ^{212}Pb, designed an assembly whereby the radon producing source is placed inside the collector chamber or container. Instead of using ^{228}Th only as a source is the present invention flexible and can able to use pure ^{224}Ra or a combination of ^{228}Th or ^{224}Ra as source, or even their precursor isotopes (Figure 1).

The assembly of the present inventions can be made very compact and very simple, allowing for a shippable and disposable ^{212}Pb-generator unit. In the present context is assembly, diffusion generator and system are used interchangeably. The described assembly or system may therefore be termed a single chamber diffusion generator for ^{212}Pb.

Thus, an object of the present invention relates to a method for obtaining a container comprising ^{212}Pb on the inner walls comprising the steps of providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided, allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, and/or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly, removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. Examples of such containers or assemblies are described in the examples of the present disclosure and can also be seen in figures 2-5.

An aspect of the invention relates to a method of obtaining a ^{212}Pb solution comprising obtaining the above container comprising ^{212}Pb on the walls and collect the ^{212}Pb in a solution. The ^{212}Pb can be collected in a solution that is in the container before the ^{212}Pb is generated or using a solution that is introduced to the container after the ^{212}Pb has been generated, and then collected. The collection can be done for example using a syringe.

A further object of the present invention relates to an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

Yet another object of the present invention relates to a single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

A huge advantage with the described assembly (or also defined herein as a container, system or a generator) is the ability to supply ^{212}Pb without the activity level is dictated by the short (10.6 h) half-life of ^{212}Pb. With the described system it is possible to produce a diffusion generator in a centralized production facility and ship it to the end user. A portable disposable generator could be made and shipped to *e.g.* a hospital from one end or the world to the other. For such a disposable unit, a pure ^{224}Ra (without ^{228}Th) is preferable as this would become inactive after 40-50 days approximately avoiding generation of long-lived radioactive waste. Such a diffusion source will steadily produce ^{220}Rn/^{212}Pb in a fashion dictated by the half-life of ^{224}Ra (Table 1 and Figure 1). The container, comprising the ^{212}Pb precursor isotope source, will produce ^{212}Pb due to the nature of decaying isotopes. The amount of ^{212}Pb deposited on will depend on several factors including the choice of ^{212}Pb precursor isotope source and time. The time is an important factor. An object of the invention relates to a method for preparing a substantially pure ^{212}Pb solution, the method comprising obtaining the assemblies and containers described herein, wherein the ^{212}Pb precursor isotope source is kept in the sealed assemblies and containers for a given time, the ^{212}Pb precursor isotope source is isolated or removed without coming into contact, and the ^{212}Pb on the walls are then collected by adding a solution that is suitable for collecting the ^{212}Pb. The time that the ^{212}Pb precursor isotope source is kept in the assemblies and containers of the present invention can be from minutes, to hours, to days, to years, depending on the choice of ^{212}Pb precursor isotope source and the amount of ^{212}Pb needed. The time can be at least one day. The time can be at least one day. The time can be at least two days. The time can be at least four

days. The time can be at least a week. The time can be at least two weeks. The time can be at least two weeks. The time can be at least a month. The time can be at least a year.

^{212}Pb is a member of the thorium natural radionuclide series and can be found in materials containing ^{232}Th ($t_{1/2}$=1.4x10^{10} years). The ^{212}Pb precursor can therefore be chosen based on the intended use. A precursor with longer half-life can be chosen to generate an assembly or system that that will act as a ^{212}Pb generator for continuous production over a longer period of time. Alternatively, an isotope with a shorter half-life be used is the intended use for example is at a hospital or similar where generation of long-lived radioactive waste can be problematic. Naturally a mix of different precursors will therefore also be relevant and also where specific assemblies are needed for the generation of a specific amount of ^{212}Pb over a specific period of time.

Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra. Thus, in the following ^{212}Pb precursor isotope is defined as a mother nuclide, grandmother nuclide, great grandmother nuclide etc. for ^{212}Pb, *i.e.* ^{216}Po, ^{220}Rn, ^{224}Ra ^{228}Th, ^{228}Ac, ^{228}Ra, ^{232}Th.

The decay of these radioisotopes can be seen in figure 1 which clearly indicate the possibility of creating a ^{212}Pb precursor isotope source with different decay profiles and different combinations of precursor isotopes will be able to generate ^{212}Pb at different rates over different periods of time.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra. The source can also be each of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra individually, but due to the decay will a mixture naturally over time occur because ^{232}Th will decay to ^{228}Ra and so on. The key is that the gaseous ^{220}Rn is produced because it will diffuse from the source and later settle on the inner walls of the container as ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{228}Th measured as % radioactivity relative to ^{212}Pb.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{228}Th. The ^{212}Pb activity may vary from typically 0% to 114% of the ^{224}Ra precursor activity in the generator depending on the ingrowth status. The ^{212}Pb activity can be at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 10 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 10 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 20 % of the ^{224}Ra

precursor activity. The ^{212}Pb activity can be at least at least 30 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 40 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 50 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 60 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 70 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 80 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 90 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 100 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be at least at least 110 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 20 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 30 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 40 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 50 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 60 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 70 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 80 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 90 % of the ^{224}Ra precursor activity. The ^{212}Pb activity can be up to 100 % of the ^{224}Ra precursor activity.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is ^{224}Ra that has at least 90 %, such as at least 80 %, such as at least 70 %, such as at least 60 %, such as at least 50 %, such as at least 40 %, such as at least 30 %, such as at least 20 %, such as at least 10 % ^{224}Ra measured as % radioactivity relative to ^{212}Pb.

The assembly working as a ^{212}Pb generator unit can be mass produced in a centralized production facility and shipped to end users for application in production of radiopharmaceuticals. It can also be adapted and used for large scale centralized production of ^{212}Pb. Thus, the amount of radioactivity in the assembly can adjusted according to its intended use. In one or more embodiments of the invention will the total amount of radioactivity in the single chamber container assembly therefore can be 1 kBq – 100 GBq, such as 1 kBq – 10 MBq, such as 100 kBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 kBq – 100 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 kBq – 10 MBq. The total amount of radioactivity in the single chamber container assembly can be 100 kBq – 10 MBq. The total amount of radioactivity in the single chamber container assembly can be 1 MBq – 1 GBq. The total amount of radioactivity in the single chamber container assembly can be 10 MBq – 10 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 MBq – 1 GBq. The total amount of radioactivity in the single chamber container assembly can be 1 GBq – 100 GBq.

In one or more embodiments of the invention will the amount of ^{212}Pb radioactivity in the single chamber container assembly therefore can be 1 kBq – 100 GBq, such as 1 kBq – 10 MBq, such as

100 kBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq. In one or more embodiments of the invention will the amount of ^{212}Pb precursor isotope source radioactivity in the single chamber container assembly therefore can be 1 kBq – 100 GBq, such as 1 kBq – 10 MBq, such as 100 kBq – 10 MBq, such as 1 MBq – 1 GBq, such as 10 MBq – 10 GBq, such as 1 MBq – 1 GBq, such as 1 GBq – 100 GBq.

The ^{212}Pb precursor isotope source can be in different forms, sizes and shapes depending on the application type. Thus, in one or more embodiments of the invention the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$. The ^{212}Pb precursor isotope source can also be in a dry form or in a liquid solution, such as an aqueous solution or a dispersion. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH. The pH can be 1-14, such as pH 1-6, pH 2-6, pH 2-8, pH 4-8, pH 5-7, pH 6-8, pH 7-8, pH 7,2, pH 8-10, pH 8-12, or pH 10-14.

The solution can be an aqueous solution. The solution can be a 0,1M aqueous HCl solution. This solution can also be used to dissolve the ^{212}Pb on the walls of the assembly.

The assembly working as a generator system may be used for preparing single patient dosing or for multiple patient dosing, or even for industrial use. The amount of radioisotope can therefore be adjusted depending on the application of the assembly.

The ^{212}Pb precursor isotope source can be placed on the rod, either directly or on a strip attached to the rod, typically in a very small liquid volume. In one or more embodiments of the invention the ^{212}Pb precursor isotope source is deposited on a strip or sphere that is made of a material suitable for application of a liquid. Such liquid can be in the amount of 1 µl to 1 ml, such as 1 µl to 10 µl, such as 1 µl to 100 µl.

When the container, which can be a vial, can be empty or contain a small volume of liquid in the bottom, that is not touching the source. In one or more embodiments of the invention the container comprises an aqueous or an oil solution.

It is important that the source does not drip or chip of in a fashion that causes cross contamination of the inner surfaces of the collector unit (container) with source material and that the source and source holder can be removed and or withdrawn from the collector without causing cross contamination by contact.

In one or embodiments the source is surrounded by a grid or encapsulated in a porous material to reduce risk of cross-contamination. This encapsulation can be a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

Thus, in one or more embodiments of the invention the container does or does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion. The container may comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source, and the gas permeable barrier impervious to the ^{212}Pb precursor isotope source can be in contact with the ^{212}Pb precursor isotope source. In one or more embodiments of the invention the single chamber container assembly is gas tight.

Figure 2 shows an example of the single chamber container assembly where the container (the first part) is connected with a cap and a rod attached to the cap is used to hold the ^{212}Pb precursor isotope source (the second part) without having this source touch an inner wall of the container during the entire process.

In one or more embodiments of the invention the ^{212}Pb precursor isotope source can therefore be bound to a non-radioactive material, such as particles or a holding material. These can ensure that the source does not contaminate the container. The ^{212}Pb precursor isotope source can be deposited on a strip, sphere or a rod which is made of material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers. The strip or sphere can be attached to the second part or be contained or comprised in the second parts, which comprises means for holding the strip or sphere. Such means can for example be a rod.

In one or more embodiments of the invention the second part comprises, optionally, a rod that is attached to the means for opening and closing the container. The means for opening and closing the container can be a cap, cover or a lid which can be made of a material selected from the group consisting of rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers, cellulose ion exchange resin, natural mineral, polymer. Alternatively, the source is attached to a material placed onto the cap with or without being adhered to the cap. If the cap is placed on the bottom, the source material can be simply placed onto the interior of the cap without touching the ^{212}Pb collector part and kept in place by gravitation. In such case the generator unit should be stored and handled in position whereby cap with the source is always kept at the bottom.

The means for opening and closing the container can comprise the ^{212}Pb precursor isotope source. The ^{212}Pb precursor isotope source can be placed on a sponge, a wool or another substance that is capable of keeping the ^{212}Pb precursor isotope source in the means for opening and closing the container. The wool can be a quartz wool. The wool can also be a mineral wool. The wool can also be a glass wool. The substance that is capable of keeping the ^{212}Pb precursor isotope source in the means for opening and closing the container can be attached by glue, double-sided mounting tape or other means for attachment.

In one or more embodiments of the invention the second part comprises a syringe, or wherein the rod is the syringe. The means for holding can be deposited on a strip or sphere which is made of

material that is selected from the group consisting of paper, plastic, metal, ceramic, and natural or synthetic fibers cellulose ion exchange resin, natural mineral, polymer.

In one or more embodiments of the invention the syringe tip has been pushed through a rubber cap. An alternative design is where the second part is a rubber cap, or septum of another material permeable, and preferential self-sealing, with a syringe tip, with means for holding the ^{212}Pb precursor isotope source attached to the cap or to the inner walls of the container. In this case will user of the assembly be able to dissolve the ^{212}Pb from the inner walls of the container in an aqueous solution though a syringe that is pushed through the cap. The resulting ^{212}Pb in aqueous solution can afterwards be collected by the same syringe which will generate the option of working in a GMP environment which can be directly applied for patient use. Thus, in one embodiment the ^{212}Pb precursor isotope source be withdrawn into a capsule or similar allowing the container to be washed e.g., by using a solution transferred via a syringe through a rubber septum, without having to disassemble the two units. In another embodiment the assembly can be autoclaved, and the solution be of a physiological acceptable composition containing a chelator for disease targeting allowing withdrawal into a syringe and direct infusion with or without the use of a sterile syringe filter. In one embodiment the assembly including all subunits is autoclavable and with a syringe permeable zone on the cap allowing aseptic extraction of ^{212}Pb from the assembly.

After a few hours or days of operation the assembly with the ^{212}Pb precursor isotope source can be used for producing ^{212}Pb by retracting the ^{212}Pb precursor isotope source, e.g., by changing the cap with the attached ^{212}Pb precursor isotope source to a new cap without radioactivity and washing the inner surface with a suitable solution to dissolve surface deposited ^{212}Pb and progenies. Since the ^{212}Pb solution is free from long lived predecessor radionuclides it can be used directly without further chemical processing to label carrier molecules for e.g. cancer therapy.

The ^{212}Pb precursor isotope source can associated with a needle, rod or a strip of a material of which ^{212}Pb precursor isotope source is attached to allow diffusion of ^{220}Rn. The source may or may not contain a holder for the radioactive part and a grid or ring or similar surrounding the source to prevent cross contamination when the ^{212}Pb precursor isotope source is withdrawn from the container. In one embodiment it may be attached to a screw cap that can be used to close the container. The ^{212}Pb precursor isotope source can be isolated from the container by withdrawing the source into a cover. This will ensure that the source does not cross contaminate the inner walls of the container while the ^{212}Pb is extracted, and also limit risk of exposure to the user of the assembly. It is important that after a period of decay the ^{212}Pb precursor isotope source and the ^{212}Pb adsorbed onto the vial inner surfaces can be separated by withdrawing the ^{212}Pb precursor isotope source form the container, e.g. by replacing the screw cap of which the source is attached by a rod or similar with a standard gas tight screw cap. Thus, In one special embodiment is the ^{212}Pb precursor isotope source equipped with a retractable radioactive source that is withdrawn

into the cap similar to a “click pen system” or similar for isolating the source from the generator units interior surfaces and thus not require the disassembling and replacement of the cap (e.g. Figures 2 and 4). Thus, the second part of the assembly can comprise a piston that can be in open and closed positions. The second part of the assembly can also comprise a chamber with a gas tight o-ring seal. In one or more further embodiments the assembly comprises a gas and liquid tight lid or valve in the second part.

The second part of the assembly can, optionally, comprise a needle, rod or strip which may be supplied with a small ball of a material that can absorb radium or thorium including glass wool, quartz wool, mineral wool, metal, paper, cotton, stearate or another fatty acid, metal, cellulose, natural mineral, polymer, ion exchange resin, or other fibrous material. The composition of the holder of the precursor isotope should be chosen with care according to the known affinity of radon for various materials. A material that ^{228}Th and or ^{224}Ra has a good adsorption or absorption to and ^{220}Rn has a low affinity for would be suitable. The container can be made of a glass (including quartz), polymer and or metal, such as a glass vial, with a screw cap or similar, whereby the source is attached to the screw cap. The container (or assembly) can be a glass flask placed up-side down and with for example quartz wool with ^{224}Ra or ^{228}Th placed in the center of the inside of the cap. ^{212}Pb can be produced by unscrewing the flask standing up-side down from the cap with the source, and thereafter washing the interior of the flask with a solution to dissolve ^{212}Pb. The container can have a volume of 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml. The volume will depend on the use, where single use generally will be smaller and industrial batch containers will be larger.

Minimizing risk of cross contamination is important and the assembly has to be designed so that the ^{212}Pb precursor isotope source does not come into contact with the inner walls of the container. Thus, in one or more embodiments of the invention the container is substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container. The definition of substantially free depends on use of the ^{212}Pb produced in the assembly. In one or more embodiments of the invention is “substantially free” defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % radioactivity relative to ^{212}Pb. In one or more embodiments of the invention, the substantially free refers to the purity of ^{212}Pb vs ^{224}Ra in a solution from the walls of the container. This purity can be better than 95 %. This purity can be better than 98 %. This purity can be better than 99 %. This purity can be better than 99,5 %. This purity can be better than 99,8 %.

The container is surrounding, but not touching, the ^{212}Pb precursor isotope source. This should be made of an appropriate material, for example glass, plexiglass, metal, ceramics, polymer including polypropylene and Teflon or other materials suitable for allowing deposition of ^{220}Rn and/or ^{212}Pb on its inner walls and allowing ^{212}Pb to be dissolved when washed with a suitable solution for

further use in radiolabeling. A solution can be used to wash the inner walls of the container to extract radionuclides, mainly ^{212}Pb and progenies. It may be present during the ^{212}Pb production period in the assembly or be applied after the ^{212}Pb precursor isotope source has been removed or withdrawn. In one embodiment the solution and an acidic or alkaline solution that can be transferred and neutralized before use for administration to a patient. In one embodiment the solution may be water of a suitable purity for pharmaceutical use. Solution volume of 1 ul to 1 liter for single dosing, e.g. 100 ul to 10 ml, and 1 ul to 10 liter or higher for multiple dosing may be used.

The container may or may not contain a surface film on the inner surfaces or some liquid to assist in collecting the diffusion product. This surface film can for example be a coating. Size and volume may be in microliter to ml for single dosing units and in microliters to tens of liters or higher for multiple dosing. The inner walls of the container can be coated. This coating can ensure that ^{212}Pb settles in an optimal way. In one or more embodiments of the invention the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb. It is also possible that the inner walls are coated with one or more compounds where a complex with ^{212}Pb is needed. In one or more embodiments of the invention the inner walls of the container are coated with a chelator capable of chelating ^{212}Pb. This chelator can be TCMC or a variant hereof. The coating may be a film of salt or other suitable material on the inner walls.

In a special embodiment the container is washed directly with the reaction solution containing the complexing agent to yield a radiolabeling solution which after a suitable reaction time can be used directly for therapeutic purposes. In one embodiment the final product solution is autoclaved and or sterile filtered before administration to a subject in need thereof.

In one embodiment the assembly can be attached to a flushing and filtering circuit whereby when the source is retraced from the chamber a reservoir of a solution is connected and an outlet with a sterile filter and a syringe or vacuum pump is attached to flush the chamber and collect the flushing solution, *e.g.*, in similar fashion as for ^{99m}Tc-generators.

In general, surface ratios between precursor source holder and the collector chamber inner surfaces should be optimized so that as much as possible of the generated ^{212}Pb settles on the collector chamber surfaces. The surfaces may be smooth, or porous or may contain structures to increase surface area relative to the diffusion subunit, container or assembly.

The production can be a production period of 5 hours, 10, hours, 20 hours or more. Afterwards the source may be withdrawn from the chamber into a tube-shaped holder or similar with a gas and liquid tight lid in the bottom that closes when the source is completely withdrawn. This allows for addition of a washing solution, *e.g.*, by a syringe, or activation of a flushing and collecting circuit *e.g.* similar to that of a ^{99m}Tc generator.

In a special embodiment the single chamber diffusion unit has its ^{212}Pb precursor isotope source as a film on the inside surfaces of the assembly and has the ^{212}Pb collector unit (container) inserted into the source covered surfaces without touching these, *i.e.* a reverse configuration compared to what is shown in figure 2.

In another embodiment the diffusion generator is subject to temperature manipulation, either elevated or reduced temperature vs 20 °C.

The use of the invention for includes in the production of radiopharmaceuticals, medical devices and or standardization sources for ^{212}Pb. The assembly of the present invention can be used to generate a ^{212}Pb standard for calibrations.

In one or more embodiments of the invention is the assembly of the present invention comprised in kit with the ^{212}Pb precursor isotope source, and a solution containing a chelator, and a compound that for use in therapy. Such compound can be a nano- or microparticle. In one embodiment such a kit will contain a ^{212}Pb precursor isotope source, a solution for washing the inner walls of the container and a solution or dry form of a carrier compound, for example a chelator, micro- or nanoparticles.

Tables

Table 1. Main radiation properties of the ^{224}Ra series.

Radionuclide (half-life)	Alphas and betas (mean energy in MeV)	X-rays and gammas Energy and % abundance
^{224}Ra (3.6 days)	α 5.6	241 keV, 4.1%
^{220}Rn (55.6 s)	α 6.3	
^{216}Po (145 ms)	α 6.8	
^{212}Pb (10.6 h)	β 0.1	75 keV, 10.3% 77 keV, 17.1% 87 keV, 6.0% 90 keV, 1.5% 239 keV, 43.6% 300 keV, 3.3%
^{212}Bi (1 h)	α 6.1 × 0.36 (2.2 MeV effective[1]) β 0.7 × 0.64 (0.4 MeV effective)	727 keV, 6.7% (4.3% effective)
^{212}Po (299 ns) (64% branch)	α 8.8 (5.6 effective)	
^{208}Tl (3.1 min) (36% branch)	β 0.6 (0.2 MeV effective)	75 keV, 3.4% (1.2% effective) 511 keV, 22.6% (8.1% effective) 583 keV, 85.0% (30.6% effective) 860 keV, 12.5% (4.5% effective) 2615 keV, 99.8% (35.9% effective)

[1]Average per ^{224}Ra transformation due to branching. Only X-rays or gammas above 1% effective abundance accounted for. Adds up to a total effective energy of approximately 26.5 MeV of alpha of 0.7 MeV of beta per complete decay of a ^{224}Ra atom via progenies to a stable ^{208}Pb atom.

Table 2. A pure ^{212}Pb source with initial 100 MBq ^{212}Pb kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	23.1	4.4	0.92	0.192

Table 3. Lead-212 production from a source with initial 100 MBq ^{224}Ra kept sealed and emptied for ^{212}Pb only once.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	72.9	63.4	53.1
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	51.0	44.4	37.2

Table 4. Lead-212 production from a source with initial 100 MBq ^{224}Ra source emptied for ^{212}Pb every 24 h.

Time	24 h	48 h	72 h	96 h
^{212}Pb (MBq) total	70.3	58.2	48.1	39.8
70% extraction recovery (MBq ^{212}Pb) in final product	49.2	40.7	33.7	27.9

The following figures and examples are provided below to illustrate the present invention. They are intended to be illustrative and are not to be construed as limiting in any way.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the decay of ^{232}Th to its progenies. The decay type (alpha or beta) is indicated and so is the half-lives. These half-lives are important because they dictate the decay rate and are therefore also key in deciding the optimal mix of isotopes as ^{212}Pb precursor isotope source for the production of ^{212}Pb.

Figure 2A shows a figure of the single chamber container assembly with the container (A), the a ^{212}Pb precursor isotope source (B) that generates the ^{220}Rn gas which is released into the single chamber container assembly and after decay settled as ^{212}Pb onto the inner walls of the container (C). The upper part of the single chamber container assembly (D) is the second part which comprises the ^{212}Pb precursor isotope source and in this case a cover/cap with a rod attached pointing towards the centre of the container thus enabling ^{212}Pb precursor isotope source release of ^{220}Rn into the container. Figure 2B shows a situation where the ^{212}Pb precursor isotope source (B) has been withdrawn into a gas tight seal that ensures that no ^{220}Rn is released into the container. The ^{212}Pb precursor isotope source can also be removed entirely from the assembly.

Figure 3 shows picture of a crude version of the generator system based on a 3 ml v-vial with an membrane inserted open top screw cap penetrated by a syringe tip (with position fixed by tape on top of screw cap) and with a strip of laboratory bench paper attached to the syringe tip (left picture shows the ^{212}Pb precursor isotope source and container). The ^{212}Pb precursor isotope source is placed onto the strip by a pipette before the screwcap with the source is carefully attached to the vial (right picture). It is very important that the source is not touching the vial when assembling and disassembling the unit to avoid cross-contamination.

Figure 4. An example of a single chamber diffusion generator for ^{212}Pb with a retractable source simplifying washout of ^{212}Pb from the inner surfaces by having syringe permeable zones on the lid supplied with septum, a syringe could be used for washing of the interior surfaces without radionuclide cross contamination when the unit is put in closed position.

Figure 5. Top picture shows a 100, 50 and 10 ml generator unit for ^{212}Pb production. Bottom pictures shows the cap with quartz wool in the center of the inner surface. The ^{212}Pb precursor nuclide solution can be placed onto the quartz wool and the flask mounted for up-side-down

storage to produce ^{212}Pb deposited on the flask' inner surface generated via ^{220}Rn diffusion from the precursor source material.

EXAMPLES

Example 1 - Calculation of the relative ^{212}Pb daughter nuclide level at various time points

Background. The development and use of pure ^{212}Pb in therapeutic radiopharmaceuticals is hampered by the short half-life (10.6 h) of the radionuclide making it almost impossible to produce a product in a centralized fashion and shipped to the end user. If ^{224}Ra is used as a short-term generator for ^{212}Pb the level of ^{212}Pb activity can be maintained essentially according to the half-life of ^{224}Ra, which is 3.6 days. The variation in ^{212}Pb level in a sealed source of pure ^{224}Ra is shown.

Method: The ingrowth of ^{212}Pb from a pure ^{224}Ra source were calculated using a universal activity calculator.

Results: Table 2 shows the amount of ^{212}Pb at various time points after the production of a pure (^{224}Ra-free) pharmaceutical solution and storage in a gas tight container. As can be seen the pure ^{212}Pb source rapidly decays and lose more than 75% per 24 h. Table 3 shows the amount of ^{212}Pb present in a sealed source of ^{224}Ra at the same time points. As can be seen the ^{212}Pb activity is maintained at a high level (> 50%) at least up to 96 h.

Table 4 shows the effect of "milking" a ^{224}Ra precursor-based generator for ^{212}Pb several times during a 96-h period.

The data also shows that significant amount of daughter nuclide is present within a relatively short time frame when starting with pure ^{224}Ra. It is noteworthy though that the ratio of ^{212}Pb to ^{224}Ra in the solution reaches 1 after 36 hours and thereafter gradually increases to about 1.1 of which is kept for the rest of the time until complete decay. In conclusion, using ^{224}Ra as a source for ^{212}Pb makes the logistic of centralized production and shipment to end users possible providing an easy way to extract the ^{212}Pb from ^{224}Ra exist.

Example 2 - Preparation of radionuclides and counting of radioactive samples

In the following, all work with the concentrated radioactive preparations including evaporation of solvent etc was performed in a glove-box. A source of ^{228}Th in 1 M HNO3 was acquired from a commercial supplier. Ac-resin was obtained from Eichrom Technologies LLC (Lisle, IL, USA) in the form of a pre-packed cartridge.

Radium-224 was made from ^{228}Th bound to Actinide resin (Eichrom Technologies, LLC) by eluting a column containing actinide resin with immobilized ^{228}Th with 1 M HCl. The eluate was purified on

a second Ac-resin column and the eluate evaporated to dryness using an evaporation vial with a cap with gas inlet and outlet placed in a heater block at approximately 110 ◦C and a gentle stream of nitrogen gas to evaporate of the solvent. When the evaporation vial was empty from solvent it was added 0.1 M HCl to dissolve the residue, typically 200-400 µl. Typically, more than 70% of the ^{224}Ra present in the ^{228}Th source could be extracted and purified using the described methods.

Radioactive samples were counted on a Cobra II Autogamma counter (Packard Instruments, Downer Grove, IL, USA). During extraction of ^{224}Ra from the ^{228}Th source, a CRC-25R dose calibrator (Capintec Inc., Ramsey, NJ, USA) was used.

Example 3 - Determining net count rate for ^{212}Pb in a ^{212}Pb/^{224}Ra mixture before radioactive equilibrium has been reached

After more than 3 days, i.e., “equilibrium” a sample kept gas tight will for practical purposes have 1.1 times ^{212}Pb vs ^{224}Ra.

In a gas tight unit regardless of whether ^{212}Pb is at or lower than equilibrium it can be assumed that this is reached after 3 days since surplus ^{212}Pb is reduced by 99% and the ingrowth of ^{212}Pb from ^{224}Ra is practically complete vs. “equilibrium”.

Using the Cobra II Autogamma counter with a counting window setting from 70-80 KeV gives mainly the ^{212}Pb with very little contribution from other radionuclides in the ^{224}Ra series. Radium-224 must be indirectly counted when the initial ^{212}Pb has vanished and equilibrium between ^{224}Ra and ^{212}Pb has been reached (after approximately 3 days). This indirect counting requires the sample to be stored in a relatively gas tight containers as otherwise the ^{220}Rn may escape preventing the radionuclide equilibrium of 1.1 between ^{212}Pb and ^{224}Ra to be reached.

Since sampling and counting may be separated by some time, the net count rate for ^{212}Pb can be adjusted for decay to determine the net ^{212}Pb count rate at the time of sampling. By storing ^{212}Pb samples for a week or longer and remeasure, the amount of ^{224}Ra contaminant can be determined as activity after about 110 hours of storage would not be ^{212}Pb but must be from longer lived precursor isotope.

Example 4 - A simplified single chamber (diffusion chamber generator) assembly for ^{212}Pb production (Figure 3).

A 3 ml v-vial with an open top cap. The open top cap was supplied with a membrane permeable by a syringe tip. A syringe tip was pushed through the membrane and fixed with tape on top to lock the position of the tip with regard to the open top cap. On the syringe tip vas placed a strip of

absorbent paper about 0.5 X 3 cm by inserting the syringe tip in two holes in the strip. The paper strip was added 2-40 ul ^{224}Ra solution. Thereafter the cap was placed carefully onto the v-vial while the syringe tip and radioactive strip were not to touch the inside of the v-vial. Thereafter the assembly was standing for various time to produce ^{212}Pb via ^{220}Rn diffusion from the strip to the space surrounding the strip. The ^{212}Pb tended to settle on the inner surfaces of the v-vial. Depending on the liquid volumes used for applying the ^{224}Ra source onto the strip, there may be some condensation of liquid due to evaporation/condensation of the liquid applied. Alternatively, the source could be dried before assembling the unit to avoid any solvent condensation on the v-vial inner surfaces.

Example 5A: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a paper strip.

Methods: The assembly was assembled with ^{224}Ra placed on the strip of the diffusion subunit inserted in a v-vial according to Figure 3, and was standing for 17.5 h or more to produce ^{220}Rn and ^{212}Pb. Production of ^{212}Pb evaluation of radiochemical purity of product. At the end of the production period the whole unit was measured on a Capintec dose calibrator. The product was evaluated by separating the source from the container and cap the latter with a gas tight screw cap and measure immediately in the Capintec dose calibrator. The purity of the product was determined by measuring the collector subunit again after a few days when all the ^{212}Pb had decayed but the presence of longer-lived predecessor nuclides ^{224}Ra and ^{228}Th would have been measurable. Results: Highly purified ^{212}Pb was collected in the collector subunit with a relevant yield of 65.6% (range 62.7-69.9% n=4) and with no measurable longer-lived precursor nuclides present (< 0.5%). In conclusion: The assembly was effective in producing and collecting purified ^{212}Pb in an easy manner without need for further purification.

Example 5B: Production of ^{212}Pb with the ^{212}Pb precursor isotope source absorbed on a parafilm strip. The experiment from 5A was repeated except that a parafilm strip was used instead of paper a strip to carry the precursor isotope source.

Results: The yield of ^{212}Pb on the inner surfaces of the collector subunit (vial or container) was found to be only 19.3%. In contrast a unit with paper strip run in parallel with exact same configuration and emanation period gave a yield of 63.9%. In conclusion, the material used for absorbing and holding the ^{212}Pb precursor isotope source could greatly affect the yield of ^{212}Pb on the collector subunit or container.

Example 6: Dissolving of ^{212}Pb from the container using a solution.

Methods: The collector vial was added 0.3-0.5 ml 0.1 M HCl which was gently swirled to contact the inner surfaces with the liquid and counted in the Capintec dose calibrator. Thereafter the liquid was transferred to an Eppendorf tube and measured in the Capitec dose calibrator. The extraction yield was 74.0 % (range 70.0-76.9%, n=3) when the collector subunit (3 ml v-vial), was washed one single time with 0.3 ml 0.1 M HCl. In conclusion, ^{212}Pb absorbed onto the surfaces of the container was rapidly and with good yield dissolved by a solution useful for radiopharmaceutical processing.

Example 7: Thin layer chromatography analyses

Thin layer chromatography (TLC) was performed using chromatography strips (model # 150-772, Biodex Medical Systems Inc, Shirley, NY, USA). A small beaker with about 0.5 ml of 0.9% NaCl was used to place strips with a sample spot in. To the strip was typically added 1-4 µl of sample at approximately 10% above the bottom of the strip. After the solvent front had moved to about 20% from the top of the strip, the strip was cut in half and each half was placed in a 5 ml test tube for counting. In this system radiolabeled antibody and free radionuclide does not migrate from the bottom half while radionuclide complexed with EDTA migrates to the upper half. A formulation buffer (FB) consisting of 7.5% human serum albumin and 1 mM EDTA in DPBS and adjusted to approximately pH 7 with NaOH was mixed with the radioconjugates in ratio 2:1 for at least 5 minutes before application to the strips to determine free radionuclide. It was verified that in a test solution with free ^{212}Pb was the radionuclide was completely (> 99%) complexed by the EDTA, when mixed with FB, and would travel to the upper half of the TLC strip.

Example 8: In situ chelation of ^{212}Pb in solutions.

Background: The labeling properties of the ^{212}Pb extracted with 0.1 M HCl from the containers was evaluated. Methods: A 10:1 ratio of ^{212}Pb in 0.1 M HCl and 5 M ammonium acetate was used before addition of the chelators, resulting in a pH range of 5 – 6 for the reactions. Reaction times of 15-30 minutes at 37 °C, were tested. For PSMA-617 solutions of 5 µg per 100 µl was labeled with good yield of 96.6% as determined by TLC. Also, TCMC-conjugated Herceptin antibody solution of approximately 1.0 mg/ml was labeled with pure ^{212}Pb with a good yield of 98.9%. In conclusion: Lead-212 produced with the assembly was readily complexed with small molecular and large

molecular conjugates indicating suitability for use in production of ^{212}Pb based radiopharmaceuticals.

Example 9 - Production of ^{212}Pb from the ^{224}Ra source when unit is kept sealed and emptied only at one time point

Table 3, lower row, shows the example of an output from a diffusion generator emptied after various time points after insertion of the source of 100 MBq of ^{224}Ra into the unit. As shown the generator gives a relatively stable output of ^{212}Pb for up to 96 h.

Example 10 - Production of ^{212}Pb from the ^{224}Ra source when unit is emptied once a day for four days e.g. if used for fractionated radionuclide therapy etc.

Table 4 shows the output when the assembly is “milked” once every 24 h. The combined output is a total of 151.5 MBq of ^{212}Pb when starting with a 100 MBq source. In conclusion, the one chamber assembly is suitable for single dose as well as fractionated dose production.

Example 11 - Example of an assembly with a retractable source (Figure 2 and Figure 4)

The materials used may be of glass (including quartz), polymer, metal, ceramic or other suitable materials for pharmaceutical containers. The rod in figure 2 (piston in figure 4) slides in a tube with o rings or similar at the top to secure gas tight seal. The valve at the bottom of the rod is gas and liquid tight in the closed position for the unit.

In the open position the source will be exposed inside the container and emanate ^{220}Rn and cause deposit of ^{212}Pb onto the inner surface. In closed position the source is sealed off from the container (Figure 2B) and the container surfaces can be contacted with a suitable solution to dissolve ^{212}Pb.

In one embodiment where the cap has syringe permeable membrane, a sterile syringe with a sterile solution is used to extract the ^{212}Pb without removing the cap. When such unit has been autoclaved before the extraction of ^{212}Pb, the complete procedure can be performed in an aseptic/sterile fashion.

Example 12. Precursor nuclide placed onto quartz wool in a ^{212}Pb single chamber generator.

Methods: A flasks as shown in figure 5, was used. Flask size could vary and typically 10-100 ml flasks were used. When used as a generator the flask was turned-up-side down. The cap was

removed and inside of the center of the cap was placed quarts or glass wool. Radium-224 in solution was placed on the quartz wool and the flask was mounted onto the cap without touching the quartz wool with the flask. The unit was kept tight and stored in up-side-down position for a period of time to produce ^{212}Pb from ingrowth. After typical one to a few days the flask was unscrewed from the cap while being held up-side-down and carefully removed from the cap without touching the quartz wool. The cap with the source was combined with another flask and stored up side down for further ^{212}Pb production. The unscrewed ^{212}Pb containing flask was added a solution of 0.5-2 ml of 0.1 M HCl and the ^{212}Pb extracted from the flask by washing the interior surfaces and collected for use.

Results: Typically, 50-70 percent of the ^{212}Pb activity produced was found in the flask and by carefully washing more than 90% of the ^{212}Pb activity could be collected in the washing solution. The produced ^{212}Pb had a very high purity with ^{224}Ra being as low as 10^{-4} vs ^{212}Pb in newly extracted solutions. The product was very suitable for use in labeling of chelator-containing proteins and small molecules giving very high labeling yields, typically above 97%.

In conclusion, the data showed that quartz wool was very suitable for holding a ^{224}Ra source indicating that quartz/glass/mineral wool, metal wool etc would be suitable for this purpose. It would be possible to use the flask/ quartz wool system in upright position also providing the quartz wool is adhered to the capsule, e.g. with glue, double-sided mounting tape etc. In the current example the flask was used up-side down and the quartz wool was not adhered, but just placed and kept by gravity in position inside the cap.

Example 13. Up-side-down flask system version of single the chamber generator.

Flask based diffusion generator for labeling with ^{212}Pb.

Lead-212 generate therapeutic high-LET radiation as it decays via short-lived alpha emitting daughters resulting in an average of one alpha particle per ^{212}Pb decay. The half-life of ^{212}Pb of 10.6 hours is a limitation to its use and fast and safe production and purification procedures are required. If a ready to use product was to be produced in a centralized production facility and shipped to the end user, the activity level would be reduced to less than 25% in one day. Lead-212 based radioimmunoconjugate has been in clinical testing against peritoneal cancer using ^{212}Pb separated from ^{224}Ra in a cation exchange column and eluted in mineral acid which has to be reconstituted before radiolabeling. This method requires a significant work effort, facilities, and equipment suitable for evaporation of mineral acids etc to work up the ^{212}Pb from the ^{224}Ra generator material. An alternative generator method was developed and tested based on ^{224}Ra absorbed onto quartz wool and placed inside the centered ring of a removable cap (the generator cap), in a generator chamber. The chamber consists of a glass bottle turned upside down and the

removable cap supports the ^{224}Ra labeled quartz wool (Figure 5). When ^{224}Ra decays, the short-lived ^{220}Rn emanates from the quartz wool and causes absorption of the longer-living decay product, ^{212}Pb, onto the interior surfaces of the flask. The flask can be removed from the cap without the glass coming in contact with the quartz wool. After removing the flask from the generator cap, the flask can be rinsed on the inside with 0.1 M HCl to dissolve the ^{212}Pb deposits whereby a highly purified ^{212}Pb solution is made. The operation and washout of the generator flask is made prior to radiolabeling of NG001. The purity of ^{212}Pb vs ^{224}Ra in the solution is, when the generator is operated in a correct manner (i.e. that the source does not come into contact with the walls), better than 99.8%. The generator can be re-used by attaching a new glass bottle to the generator cap and store for typically 1-2 days for the generation of fresh ^{212}Pb.

In summary, the generator method is easier to use and less time consuming compared with ion exchange-based generators. The generator may be re-used several times (although with a decreasing capacity due to radioactive decay depending of source half-life).

Example 14: Size of collector flask,

The flask sizes of 10, 50 and 100 ml was tested (Figure 5, upper part). ^{224}Ra was added to quarts wool placed in the cap of flasks placed upside down. The % ^{212}Pb on the flask compared with the theoretical yield varied from about 40% to 60%. It tended to be an advantage to use a larger flask to cap inner surface volume to obtain high yield. In conclusion, flasks with various sizes could be used for generator purposes but a relatively large flask vs. cap seemed to improve ^{212}Pb yield as relatively less would be lost due to absorption on the cap and the source material.

Example 15: Materials for holding the source.

To hold the source material in place inside the generator, e.g., in the inner cap center, Steel wool, glass wool, quartz wool was tested with ^{224}Ra sources. The materials are porous and fluffy and allows for diffusion. A volume of 100-150 microliter of ^{224}Ra in 0.1 M HCl was deposited onto the materials placed inside the caps of 100 ml flasks. After standing for 2-3 days or more, 52-64% of the ^{212}Pb compared to ^{224}Ra present in the generator would have settled on the glass surfaces, so all the three materials would work. i.e., quartz wool averaged of 5 tests, 59.9% (range 52.1-64.4%), glass wool 54.9% and steel wool 64.1% for one test each as compared to ^{224}Ra activity in the generator. In conclusion, several different materials could be used to hold the source in the one chamber diffusion generator.

Example 16: Sources.

The radionuclides ^{224}Ra and ^{228}Th were used as sources inside the generators. The ^{224}Ra -based generator could be used typically repeatedly up to a few weeks while the ^{228}Th -based unit could be used repeatedly for several months and deliver ^{212}Pb by simply switching the glass flask with an unused one and wash the first flask to produce a ^{212}Pb solution. Yield was not significantly reduced with repeated use except for the decay of the generator radionuclide. As long as the sources are centered inside the cap to avoid contact with the glass bottle, and flasks and caps are kept dry, cross contamination from source to the glass flask was minimal. In conclusion, the single chamber diffusion unit could be used repeatedly for producing ^{212}Pb with both ^{228}Th and ^{224}Ra as the sources. Lead-212 activity on the inner glass surfaces from ^{228}Th a source was found to be on average 49.3% (range 40.9%-66.7%) from four tests.

Example 17: Preparation including heating: To heat up flask before mounting onto the cap with the source material could be a way to produce reduced pressure in the generator. The flask was heated to 90 °C in a heat chamber for at least 15 minutes and then the flask and cap was screwed tightly together to be gas tight. The generator unit was thereafter stored at room temperature causing reduced inner pressure. After 1-4 days the chamber was opened and the ^{212}Pb activity on the glass flask was measured. The yield from four tests using ^{224}Ra on quartz wool was on average 68.1% (range 60.5%-75.9%, indicating improved yield compared with previous data for normal pressure flasks (average 59.9%). In conclusion, reduced chamber pressure may improve the yield of ^{212}Pb with the one chamber diffusion generator.

Example 18: Yield of ^{212}Pb in the washout solution.

A standard solution of 0.1 M HCl was used for extracting the ^{212}Pb trapped on the inner glass surface of 100 ml flasks. The washing solution was carefully shaken and swirled to cover the inside of the flasks for about 2 minutes and then 80% of the volume was taken out and measured and compared with the total count of the flask before the washing procedure. It was assumed that the 80% volumes should be divided by 0.8 to determine the total activity in the liquid. With 0.6 ml about 85% was extracted and with 1 ml 93% was extracted with similar washing effort. From ^{224}Ra based generator on average 86.1% (range 79.4%-93.4%) for 8 tests was extracted from the glass bottles. From ^{228}Th based generator on average 86.5% (range 84.5%-88.5%) for two tests was extracted from the glass bottles. In conclusion, ^{212}Pb trapped on the inner glass surfaces in the generators are easily extracted with 0.1 M HCl.

Example 19. Radiolabeling reactivity of solutions:

The TCMC-chelator-based molecule NG001 (Stenberg et al 2020) was used for testing ^{212}Pb labeling with the generator extracted ^{212}Pb. Lead-212 in 0.1 M HCl was added sodium acetate to adjust pH to about 5.5. Thereafter, NG001 was added to 10-20 micrograms per ml. After 30 minutes reaction on 37 °C using a Thermomixer (Eppendorf, Germany), samples were withdrawn and thin layer chromatography (TLC) was performed by mixing the samples 1:2 with 1 mM EDTMP in 7.5 % bovine serum albumin solution and let it stand for 5 minutes. Thereafter 1-5 microliter was applied onto a chromatography strip (model # 150-772, Biodex) and eluted with 0.9% NaCl solution in a beaker. When the liquid front reached the top of the strip, it was cut in two halves, each placed in a tube and counted separately in a Packard Cobra II gamma counter (Packard Instruments Co Inc, USA). The data showed that after 3 hours the activity of the bottom half would make up typically >99% indicating almost quantitative yield. Blind test without the NG001 but all the other compounds would give less than 3 % on the bottom half of the strip indicating good selectivity for the TLC test. In conclusion, the ^{212}Pb extracted from the generator flask showed excellent reactivity, indicating suitability for radiopharmaceutical use.

Example 20. Radiochemical purity of extracted solutions.

Lead-212 solutions were stored for 10 days or more and recounted for measuring ^{224}Ra. The ^{224}Ra activity was decay corrected back to time 0. The ^{224}Ra vs ^{212}Pb was determined to be on average 0.045% (range 0.01%-0.13%). In conclusion, the ^{212}Pb produced from the generator had high radiochemical purity relevant for pharmaceutical use.

CLAIMS

1. A method for obtaining a container comprising ^{212}Pb on the walls comprising the steps of:

- providing an assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source,
- connecting the first part and the second part such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container and such that a single chamber container assembly is provided,
- allowing the ^{212}Pb precursor isotope source sufficient time to decay to progenies ^{220}Rn, ^{216}Po, and/or ^{212}Pb, and sufficient time for ^{220}Rn, ^{216}Po and/or ^{212}Pb to settle onto the inner walls of the single chamber container assembly,
- removing or isolating the remaining ^{212}Pb precursor isotope from the single chamber assembly without having the ^{212}Pb precursor isotope source come into contact with an inner wall of the single chamber container assembly, and
- obtaining a container comprising ^{212}Pb on an inner wall of the container and substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container.

2. An assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container, and such that a single chamber container assembly is provided.

3. A single chamber container assembly comprising a first part and a second part, wherein the first part comprises a container and the second part comprises a ^{212}Pb precursor isotope source, wherein the first part and the second part are connected such that the ^{212}Pb precursor isotope source does not come into contact with an inner wall of the container.

4. The method according to claim 1, the assembly according to claims 2-3, wherein the single chamber container assembly is gas tight.

5. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is selected from the group consisting of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and/or ^{224}Ra.

6. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{232}Th, ^{228}Ra, ^{228}Ac, ^{228}Th and ^{224}Ra.

7. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is a mixture of ^{228}Th and ^{224}Ra.

8. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb activity is 0% to 114% of the ^{224}Ra precursor activity..

9. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb activity is 0% to 103% of the ^{228}Th precursor activity..

10. The method and the assembly according to any one of the proceeding claims, wherein the total amount of radioactivity in the single chamber container assembly is 1 kBq – 100 GBq.

11. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in the form of an inorganic or organic salt, such as $RaCl_2$.

12. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is bound to a non-radioactive material, such as particles or a holding material.

13. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a dry form or in a liquid solution, such as an aqueous solution or a dispersion.

14. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is in a liquid solution that is at acidic, neutral or basic pH.

15. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere that is made of a material suitable for application of a liquid.

16. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is deposited on a sponge, a wool, a strip or a sphere which is made of material that is selected from the group consisting of quartz, glass, mineral, paper, plastic, metal, ceramic, and natural or synthetic fibers.

17. The method and the assembly according to claims 15-16, wherein a strip or sphere is attached to the second part, which comprises means for holding the sponge, the wool, the strip or the sphere, such as a rod.

18. The method and the assembly according to claim 17, wherein the second part comprises a syringe, or wherein the rod is the syringe.

19. The method and the assembly according to claim 18, wherein the syringe tip has been pushed through a rubber cap.

20. The method and the assembly according to any one of the proceeding claims, wherein the second part comprises a rod that is attached to the means for opening and closing the container.

21. The method and the assembly according to claim 20, wherein the means for opening and closing the container is a cap, cover or a lid.

22. The method and the assembly according to claim 21, wherein the cap, cover or a lid is made of a material selected from the group consisting of quartz, glass, mineral, rubber, glass, paper, plastic, metal, ceramic, and natural or synthetic fibers.

23. The method and the assembly according to any one of the proceeding claims, wherein the ^{212}Pb precursor isotope source is placed on or in a sphere, suitable for holding the source but allowing radon diffusion.

24. The method and the assembly according to any one of the proceeding claims, wherein the container comprises a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

25. The method and the assembly according to claim 24, wherein the gas permeable barrier impervious to the ^{212}Pb precursor isotope source is in contact with the ^{212}Pb precursor isotope source.

26. The method and the assembly according to claims 1-23, wherein the container does not comprise a gas permeable barrier impervious to the ^{212}Pb precursor isotope source.

27. The method and the assembly according to any one of the proceeding claims, wherein volume of the container is 1 µl to 10 liters, such as 1 µl to 1 liter, such as 100 µl to 10 ml, such as 100 µl to 100 ml.

28. The method and the assembly according to any one of the proceeding claims, wherein substantially free of the ^{212}Pb precursor isotope source on the inner wall of the container is defined as less than 3 % ^{224}Ra of the ^{212}Pb precursor isotope source, such as less than 1 %, such as less than 0,5 %, as measured as % relative radioactivity.

29. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated.

30. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a compound that comprises a chelator which can complex with ^{212}Pb.

31. The method and the assembly according to any one of the proceeding claims, wherein the inner walls of the container are coated with a chelator which is TCMC or a variant hereof.

32. The method and the assembly according to any one of the proceeding claims, wherein the container comprises an aqueous or an oil solution.

33. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a piston that can be in open and closed positions.

34. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a chamber with a gas tight o-ring seal.

35. The method and the assembly according to any one of the proceeding claims, wherein the second part of the assembly comprises a gas and liquid tight lid or valve.

36. The method and the assembly according to any one of the proceeding claims, wherein the assembly is made by a glass flask placed up-side down and with quartz wool with ^{224}Ra or ^{228}Th placed in the center of the inside of the cap.

37. A method of obtaining a ^{212}Pb solution comprising obtaining a container or assembly comprising ^{212}Pb on the walls according to any of the previous claims, and subsequently collect the ^{212}Pb in a solution.

38. A method of obtaining a ^{212}Pb solution comprising obtaining a glass flask assembly according to claim 37, unscrewing the flask standing up-side down from the cap with the source, and thereafter washing the interior of the flask with a solution to dissolve ^{212}Pb.

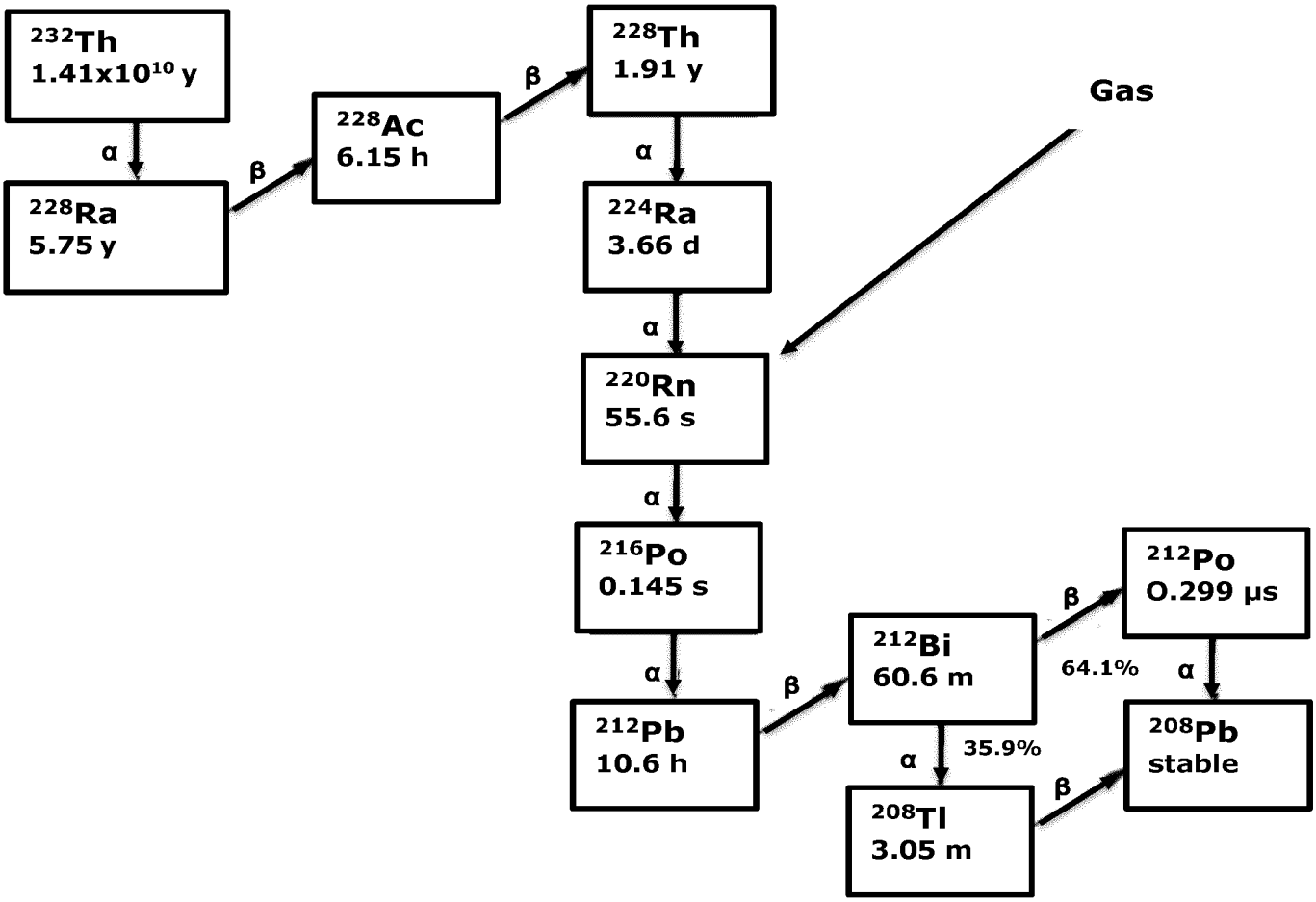

232Th
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α
228Ra
5.75 y
β
228Ac
6.15 h
β
228Th
1.91 y
α
224Ra
3.66 d
α
220Rn
55.6 s
Gas
α
216Po
0.145 s
α
212Pb
10.6 h
β
212Bi
60.6 m
64.1%
β
212Po
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α
208Pb
stable
α
35.9%
208Tl
3.05 m
β

Fig. 1

Figure 2A

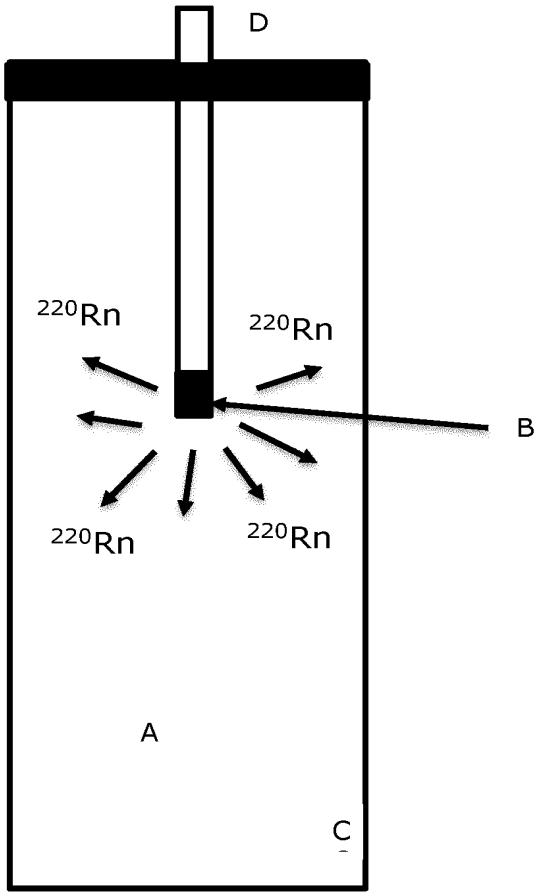


Figure 2B

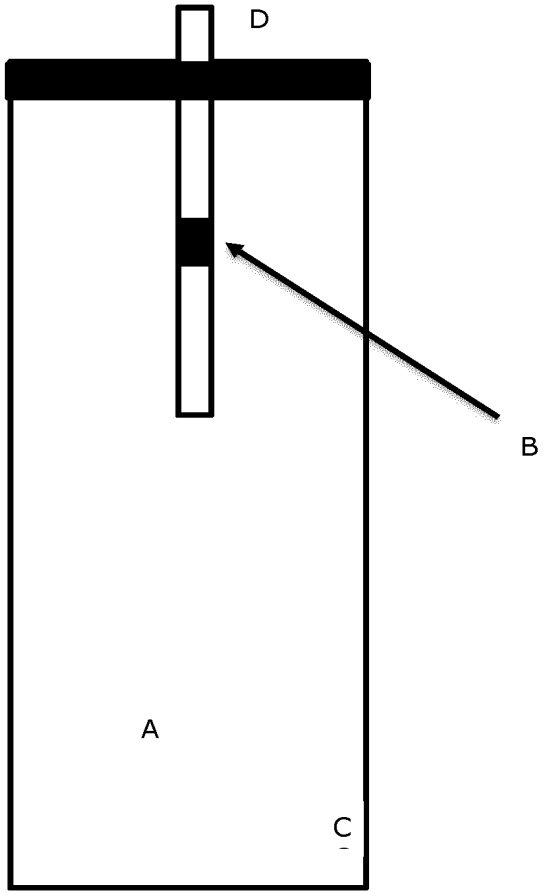


Fig 2

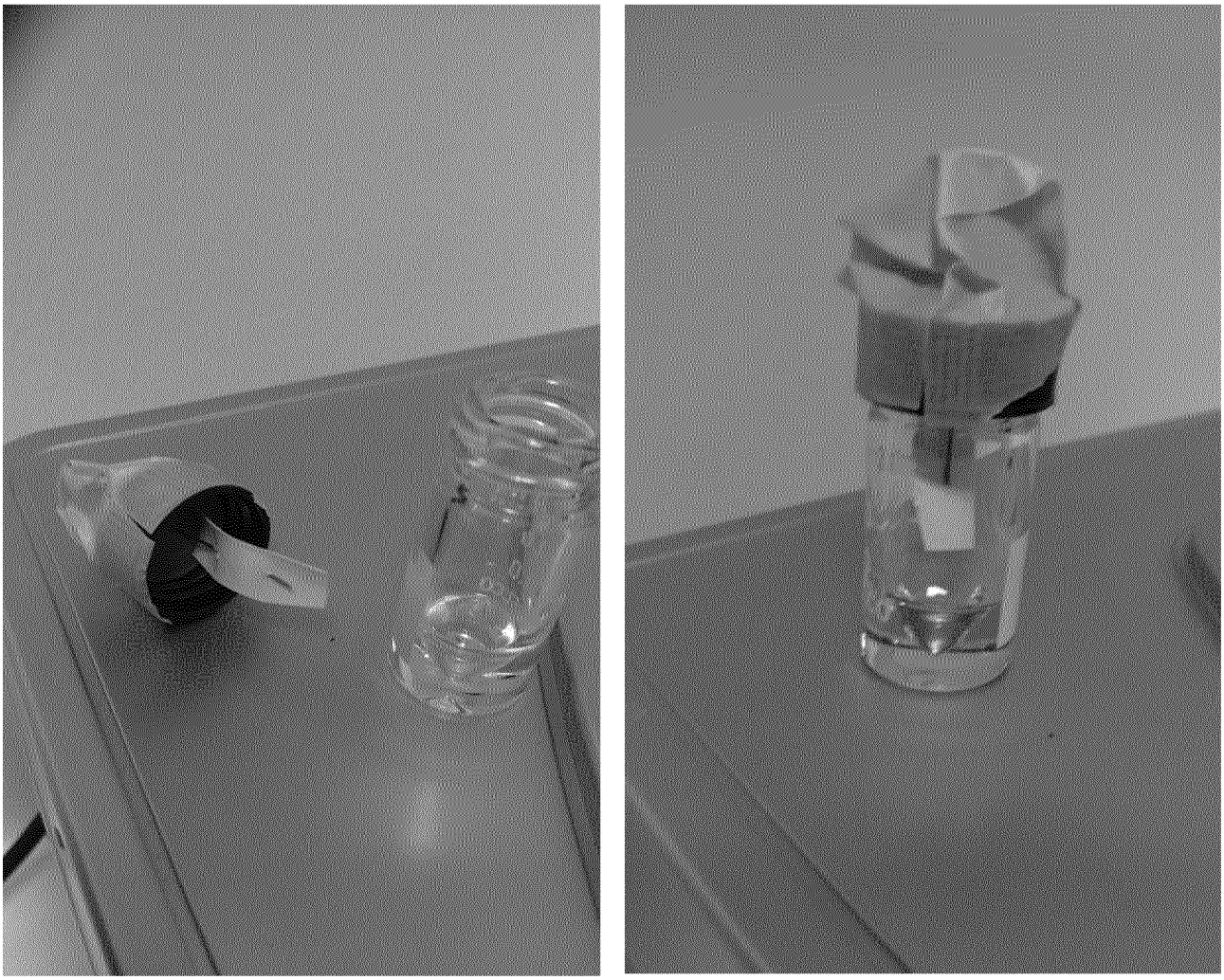


Fig 3

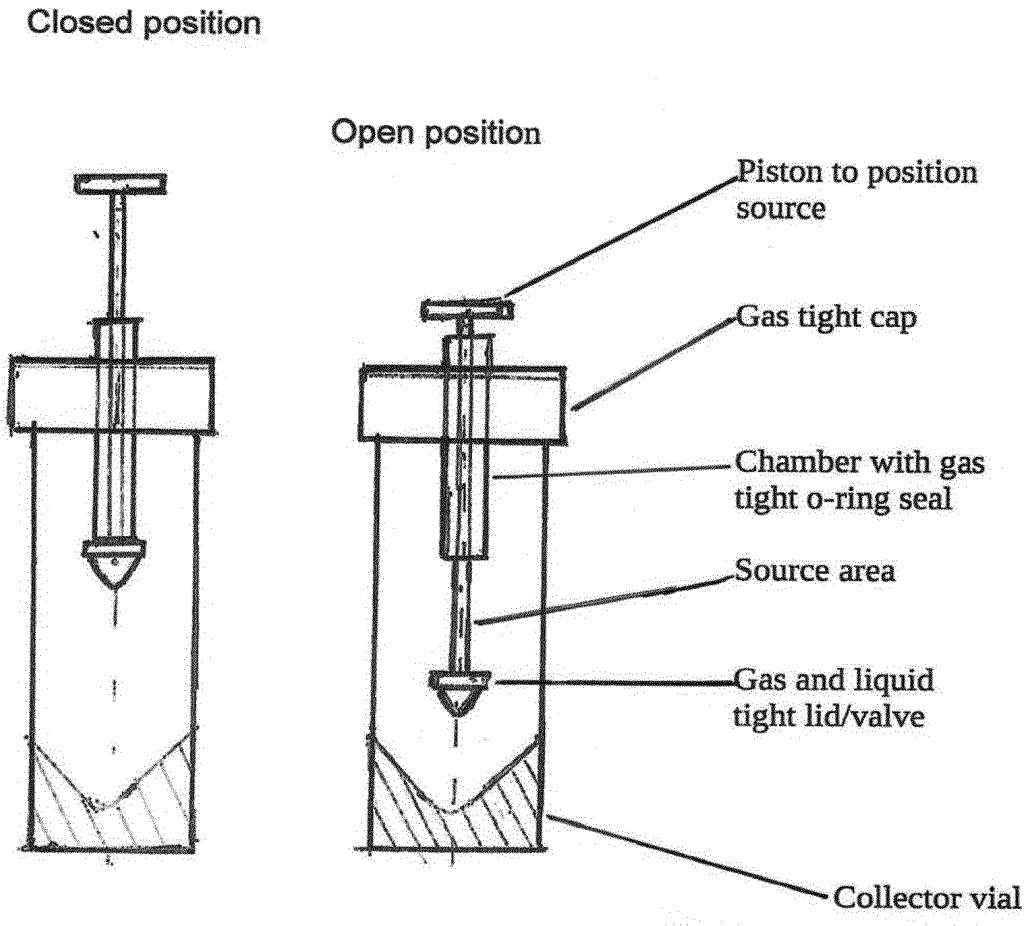

Closed position
Open position
Piston to position source
Gas tight cap
Chamber with gas tight o-ring seal
Source area
Gas and liquid tight lid/valve
Collector vial

Fig 4

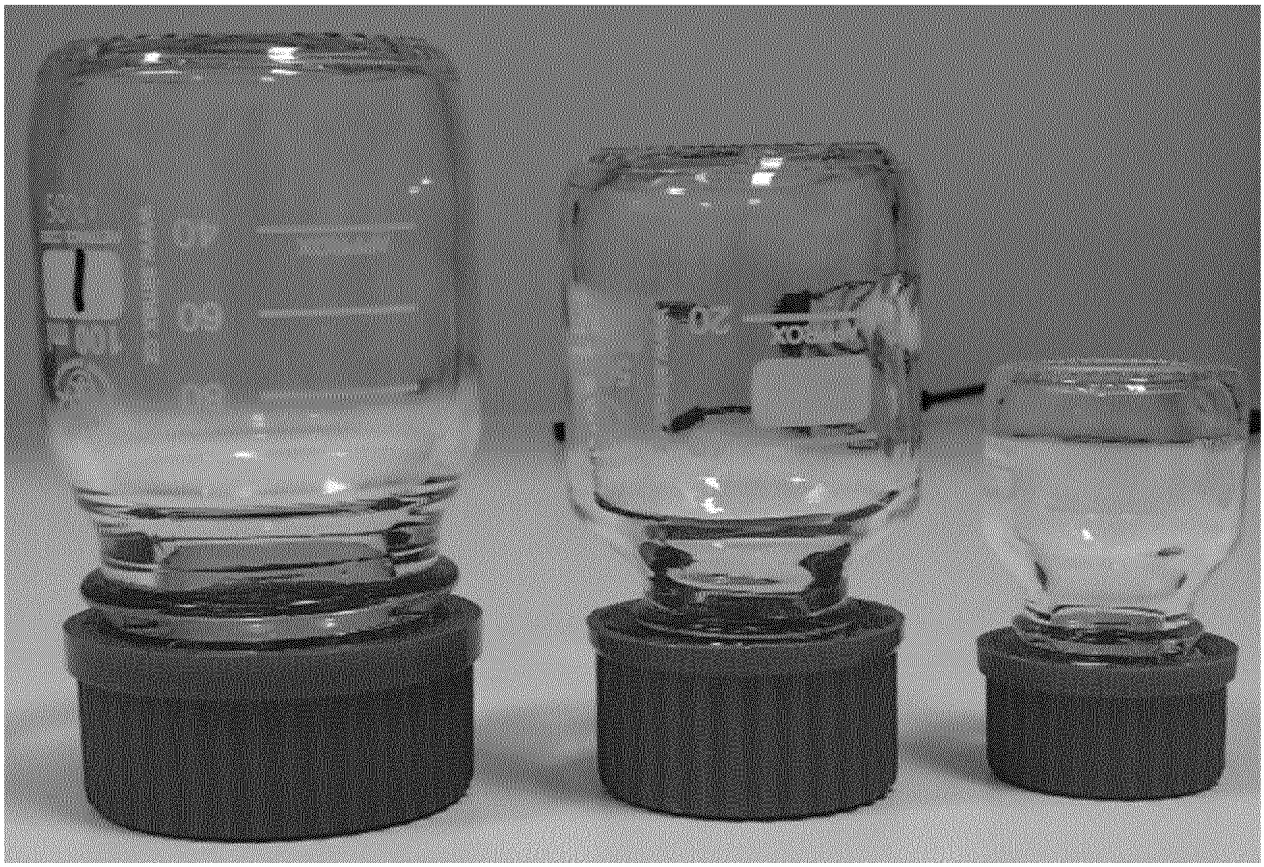




Fig 5

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Application Number	17/756802
Filing Date	June 2, 2022
First Named Inventor	Roy H. Larsen
Title	PRODUCTION OF HIGHLY PURIFIED 212PB
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	AERA001.005APC

SIGNATURE of Applicant or Patent Practitioner

Signature	/Eric Furman/	Date (Optional)	July 19, 2022
Name	Eric S. Furman	Registration Number	45,664
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

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NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

US

COMBINED DECLARATION & ASSIGNMENT (37 CFR 1.63(e))
Application Data Sheet filed previously or concurrently

Docket No.: AERA001.005APC

Title: PRODUCTION OF HIGHLY PURIFIED 212PB

Inventors: Roy H. Larsen

Declaration

This Declaration is directed to U.S. or International Application No. **17/756802**, filed June 2, 2022 and incorporating any amendments made thereto prior to the signature date of this Declaration.

As a named inventor, I declare that:

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 USC 1001 by fine or imprisonment of not more than five (5) years, or both.

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

Assignment from Inventors

WHEREAS, **above-identified inventors** (individual(s) hereinafter "ASSIGNOR") invented certain new and useful improvements, technology, inventions, developments, ideas, ornamental designs, or discoveries related to **PRODUCTION OF HIGHLY PURIFIED 212PB** (collectively hereinafter referred to as the "Work") for which an application for Letters Patent in the United States (identified above) has been filed or prepared for filing with the United States Patent and Trademark Office (hereinafter the "Application"), and ASSIGNOR desires to assign or confirm assignment of the Work and the Application to the below identified Assignee.

AND WHEREAS, **Sciencons AS,** with its principal place of business at **Gullhaugveien 7, NO-0484 Oslo, Norway** (hereinafter the "ASSIGNEE"), desires to acquire or confirm ownership of the entire right, title, and interest in and to the Application and the Work.

NOW, THEREFORE, for good and valuable consideration of which receipt is hereby acknowledged, ASSIGNOR hereby acknowledges that ASSIGNOR has sold, assigned, transferred, and set over, and by these presents does hereby sell, assign, transfer, and set over, unto said ASSIGNEE, **its** successors, legal representatives, and assigns, the entire right, title, and interest throughout the world in and to the Application and the Work, including: all provisional applications relating to the Work and the Application; all nonprovisional applications claiming priority to aforementioned provisional(s) and/or the Application, including, all divisions, continuations, continuations-in-part, and reissues, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof; and all rights of priority under International Conventions and any related Letters Patent which may hereafter be granted or filed in any country or countries foreign to the United States, all extensions, renewals, and reissues thereof.

ASSIGNOR hereby authorizes and requests the Commissioner for Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all related Letters Patent to the ASSIGNEE, **its** successors, legal representatives, and assigns.

COMBINED DECLARATION & ASSIGNMENT (37 CFR 1.63(e))

Application Data Sheet filed previously or concurrently

Docket No.: AERA001.005APC

Title: PRODUCTION OF HIGHLY PURIFIED 212PB

Inventors: Roy H. Larsen

AND ASSIGNOR DOES HEREBY acknowledge and agree that the assigned scope of the Application and the Work includes any currently recited claims, all embodiments, and all claims supported by the Application; Assignor agrees not to contest or disparage claim scope thus supported (including in any later-filed continuing patent applications) for any claims deemed patentable by any government patent office. Assignor also agrees not to challenge the validity, including as a defense to patent infringement, of any issued patent claims resulting from or based on the Work, regardless of the scope of any such claims.

AND ASSIGNOR DOES HEREBY sell, assign, transfer, and convey to ASSIGNEE, **its** successors, legal representatives, and assigns all claims for damages and all remedies arising out of any violation of the rights assigned hereby that may have accrued prior to the date of assignment to ASSIGNEE, or may accrue hereafter, including, but not limited to, the right to sue for, collect, and retain damages for past infringements of said Letters Patent before or after issuance.

AND ASSIGNOR DOES HEREBY covenant and agree that ASSIGNOR will: communicate to said ASSIGNEE, **its** successors, legal representatives, and assigns any facts known to ASSIGNOR respecting the Work; testify in any legal proceeding; assist in the preparation of any other Patent Property relating to the Application and the Work or any improvements made thereto; sign/execute all lawful papers; authorize the filing of, execute, and make all rightful oaths and/or declarations in connection with the Application and the Work including any improvements made thereto, any patent applications filed therefrom, and any continuing application filed from any of the aforementioned applications; and generally do everything possible to aid the ASSIGNEE, **its** successors, legal representatives, and assigns, to obtain and enforce proper patent protection for the Work in all countries.

AND ASSIGNOR DOES HEREBY agree that if any term or provision of this agreement becomes invalid or unenforceable, the remainder shall survive unaffected.

Legal Name of Inventor: Roy H. Larsen

Signature: RH Larsen Date: 9 June 2022

Witnessed by:

Witness Name (printed): EMANUEL OSTUNI

55725328

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**07/19/2022 07:20:44 PM ET**	**AERA001.005APC**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Derek Rahn
PATENT CENTER #	60796257	FILING DATE	-
CUSTOMER #	20995	FIRST NAMED INVENTOR	Roy H. Larsen
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Eric Furman

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Transmittal.pdf	1	Transmittal Letter	76 KB
DecAssign.pdf	2	Oath or Declaration filed	1532 KB
POA.pdf	2	Power of Attorney	2247 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Transmittal.pdf	DA7B7AAB701B649B1B68EBE19F9DFDE94BB2CA985A7C11F5

	2ED80ACE212440AF0CCD53A9E291E275B043921455FA962A0 1573E6D022423338E03AE23661A6309
DecAssign.pdf	745151B74C450CB54DB77CFD8D1DE2A07C3CC06E734C3008 2D6E25412AEB147224F3FA2F8D2303B2F1D0381E3046AEAF3 FD938F55CF75BD13183C9E55CD50A50
POA.pdf	A816E59F0835226A354472DEBC420C5AF83C5B406BE1ECF55 EC052B8ADC78516F377581EBF63C614EE1DF27DABF97F0DB 6EA982A640D3B418FFA8729632E17C4

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

DECLARATION TRANSMITTAL

First Inventor: Roy H. Larsen	**Conf. No.:** 2930
App. No.: 17/756802	**Filed:** June 2, 2022
Examiner: Unassigned	**Art Unit:** Unassigned
Title: PRODUCTION OF HIGHLY PURIFIED 212PB	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

The above-captioned application was filed without a Declaration and/or Substitute Statement. Enclosed in compliance with 37 CFR 1.53(f) are the following.

(X) Executed declaration for Roy H. Larsen;

(X) Power of Attorney and Transmittal for Sciencons AS.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 19, 2022

By: /Eric Furman/
Eric S. Furman, Ph.D.
Registration No. 45,664
Registered Practitioner
(858) 707-4000

55986180

AdvanCell
Ex. 1006 - Page 209

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT7440324

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
ROY H. LARSEN	06/09/2022

RECEIVING PARTY DATA

Name:	SCIENCONS AS
Street Address:	GULLHAUGVEIEN 7
City:	OSLO
State/Country:	NORWAY
Postal Code:	NO-0484

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	17756802

CORRESPONDENCE DATA

Fax Number: (949)760-9502

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: 949-760-0404
Email: efiling@knobbe.com
Correspondent Name: ERIC S. FURMAN
Address Line 1: KNOBBE MARTENS OLSON & BEAR LLP
Address Line 2: 2040 MAIN STREET, 14TH FLOOR
Address Line 4: IRVINE, CALIFORNIA 92614

ATTORNEY DOCKET NUMBER:	AERA001.005APC
NAME OF SUBMITTER:	ERIC FURMAN
SIGNATURE:	/Eric Furman/
DATE SIGNED:	07/19/2022
	This document serves as an Oath/Declaration (37 CFR 1.63).

Total Attachments: 2
source=DecAssign#page1.tif
source=DecAssign#page2.tif

US

COMBINED DECLARATION & ASSIGNMENT (37 CFR 1.63(e))

Application Data Sheet filed previously or concurrently

Docket No.: AERA001.005APC

Title: PRODUCTION OF HIGHLY PURIFIED 212PB

Inventors: Roy H. Larsen

Declaration

This Declaration is directed to U.S. or International Application No. **17/756802**, filed June 2, 2022 and incorporating any amendments made thereto prior to the signature date of this Declaration.

As a named inventor, I declare that:

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 USC 1001 by fine or imprisonment of not more than five (5) years, or both.

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

Assignment from Inventors

WHEREAS, **above-identified inventors** (individual(s) hereinafter "ASSIGNOR") invented certain new and useful improvements, technology, inventions, developments, ideas, ornamental designs, or discoveries related to **PRODUCTION OF HIGHLY PURIFIED 212PB** (collectively hereinafter referred to as the "Work") for which an application for Letters Patent in the United States (identified above) has been filed or prepared for filing with the United States Patent and Trademark Office (hereinafter the "Application"), and ASSIGNOR desires to assign or confirm assignment of the Work and the Application to the below identified Assignee.

AND WHEREAS, **Sciencons AS,** with its principal place of business at **Gullhaugveien 7, NO-0484 Oslo, Norway** (hereinafter the "ASSIGNEE"), desires to acquire or confirm ownership of the entire right, title, and interest in and to the Application and the Work.

NOW, THEREFORE, for good and valuable consideration of which receipt is hereby acknowledged, ASSIGNOR hereby acknowledges that ASSIGNOR has sold, assigned, transferred, and set over, and by these presents does hereby sell, assign, transfer, and set over, unto said ASSIGNEE, **its** successors, legal representatives, and assigns, the entire right, title, and interest throughout the world in and to the Application and the Work, including: all provisional applications relating to the Work and the Application; all nonprovisional applications claiming priority to aforementioned provisional(s) and/or the Application, including, all divisions, continuations, continuations-in-part, and reissues, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof; and all rights of priority under International Conventions and any related Letters Patent which may hereafter be granted or filed in any country or countries foreign to the United States, all extensions, renewals, and reissues thereof.

ASSIGNOR hereby authorizes and requests the Commissioner for Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all related Letters Patent to the ASSIGNEE, **its** successors, legal representatives, and assigns.

COMBINED DECLARATION & ASSIGNMENT (37 CFR 1.63(e))

Application Data Sheet filed previously or concurrently

Docket No.: AERA001.005APC

Title: PRODUCTION OF HIGHLY PURIFIED 212PB

Inventors: Roy H. Larsen

AND ASSIGNOR DOES HEREBY acknowledge and agree that the assigned scope of the Application and the Work includes any currently recited claims, all embodiments, and all claims supported by the Application; Assignor agrees not to contest or disparage claim scope thus supported (including in any later-filed continuing patent applications) for any claims deemed patentable by any government patent office. Assignor also agrees not to challenge the validity, including as a defense to patent infringement, of any issued patent claims resulting from or based on the Work, regardless of the scope of any such claims.

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AND ASSIGNOR DOES HEREBY covenant and agree that ASSIGNOR will: communicate to said ASSIGNEE, **its** successors, legal representatives, and assigns any facts known to ASSIGNOR respecting the Work; testify in any legal proceeding; assist in the preparation of any other Patent Property relating to the Application and the Work or any improvements made thereto; sign/execute all lawful papers; authorize the filing of, execute, and make all rightful oaths and/or declarations in connection with the Application and the Work including any improvements made thereto, any patent applications filed therefrom, and any continuing application filed from any of the aforementioned applications; and generally do everything possible to aid the ASSIGNEE, **its** successors, legal representatives, and assigns, to obtain and enforce proper patent protection for the Work in all countries.

AND ASSIGNOR DOES HEREBY agree that if any term or provision of this agreement becomes invalid or unenforceable, the remainder shall survive unaffected.

Legal Name of Inventor: Roy H. Larsen

Signature: Roy H Larsen Date: 9 June 2022

Witnessed by:

Witness Name (printed): EMANUEL OSTUNI

55725328

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/756,802	06/02/2022		1810	AERA001.005APC	38	2

CONFIRMATION NO. 2930

FILING RECEIPT

20995
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

OC000000136458899

Date Mailed: 10/03/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Roy H. Larsen, Oslo, NORWAY;

Applicant(s)

Sciencons AS, Oslo, NORWAY;

Power of Attorney: The patent practitioners associated with Customer Number 20995

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2020/084701 12/04/2020

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 20172038.0 04/29/2020
EUROPEAN PATENT OFFICE (EPO) 19213759.4 12/05/2019

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 09/29/2022

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Ex. 1006 - Page 213

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/756,802**

Projected Publication Date: 01/12/2023

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

PRODUCTION OF HIGHLY PURIFIED 212PB

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
17/756,802	Roy H. Larsen	AERA001.005APC

20995
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

INTERNATIONAL APPLICATION NO.	
PCT/EP2020/084701	
I.A. FILING DATE	PRIORITY DATE
12/04/2020	12/05/2019

CONFIRMATION NO. 2930
371 ACCEPTANCE LETTER

OC000000136458900

Date Mailed: 10/03/2022

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office, in its capacity as a Designated / Elected Office (37 CFR 1.495), has ACCEPTED the above identified international application for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above. A Filing Receipt will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE or 371(c) DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1) and (c)(2) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN BELOW.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)

06/02/2022
DATE OF RECEIPT OF 35 U.S.C.
371(c)(1) and (c)(2) REQUIREMENTS

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 06/02/2022
- Copy of the International Search Report filed on 06/02/2022
- Preliminary Amendments filed on 06/02/2022
- Information Disclosure Statements filed on 06/02/2022
- Inventor's Oath or Declaration filed on 07/19/2022
- U.S. Basic National Fees filed on 06/02/2022
- Assignment filed on 07/19/2022
- Authorize Access to Search Results filed on 06/02/2022
- Priority Documents filed on 06/02/2022
- Power of Attorney filed on 07/19/2022
- Authorization to Permit Access filed on 06/02/2022
- Application Data Sheet (37 CFR 1.76) filed on 06/02/2022

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Ex. 1006 - Page 216

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

JUELETHIA A PALMER

Telephone: (571) 272-9050

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/756,802

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	160		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	400		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	38 minus 20 =	* 18	x 50 =	900	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 240 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1730		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
17756802	

Applicant(s) Roy Larsen

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1		1			
2	1		---	---		
3	1		---	---		
4		3	---	---		
5		(1)	---	---		
6		(1)	---	---		
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38		(1)	---	---		
39			1			
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43				1		
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48				1		
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Total Indep	3		2		0	
Total Depend	37	↵	36	↵	0	↵
Total Claims	40		38		0	

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	Indep	Depend	Indep	Depend	Indep	Depend
51				1		
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/756,802	06/02/2022	Roy H. Larsen	AERA001.005APC

CONFIRMATION NO. 2930

20995
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

PUBLICATION NOTICE



Title:PRODUCTION OF HIGHLY PURIFIED 212PB

Publication No.US-2023-0014219-A1
Publication Date:01/19/2023

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

AdvanCell
Ex. 1006 - Page 220

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	17/756,802 – Confirmation Number 2930
Filing Date	June 2, 2022
First Named Inventor	Roy H. Larsen
Title	PRODUCTION OF HIGHLY PURIFIED 212PB
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	A1389.70001US00

SIGNATURE of Applicant or Patent Practitioner

Signature	/Jessamine Lee/	Date (Optional)	
Name	Jessamine N. Lee, PhD	Registration Number	61,674
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)	Sciencons AS		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 26, 2023 Electronic Signature for Theresa A. Bresnahan: /Theresa A. Bresnahan/

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
17/756,802	June 2, 2022

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[x] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 23628

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[x] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Sciencons AS

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[x] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	R M Larsen	Date (Optional)	APRIL 25TH 2023
Name	ROY R. LARSEN		
Title	MANAGING DIRECTOR		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[ ] Total of forms are submitted.

11286921.1

Electronic Acknowledgement Receipt

EFS ID:	47906317
Application Number:	17756802
International Application Number:	
Confirmation Number:	2930
Title of Invention:	PRODUCTION OF HIGHLY PURIFIED 212PB
First Named Inventor/Applicant Name:	Roy H. Larsen
Customer Number:	20995
Filer:	Jessamine Ng Lee/Theressa Bresnahan
Filer Authorized By:	Jessamine Ng Lee
Attorney Docket Number:	AERA001.005APC
Receipt Date:	26-APR-2023
Filing Date:	02-JUN-2022
Time Stamp:	13:38:32
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		A138970001US00-POA-JNL.pdf	517998 7e7c061f98a1975fc97a8f3c36f638b2858d0848	yes	2

AdvanCell
Ex. 1006 - Page 223

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	1
	Power of Attorney	2	2
Warnings:			
Information:			
	Total Files Size (in bytes):	517998	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00

CONFIRMATION NO. 2930

23628
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

POA ACCEPTANCE LETTER

OC000000057011910

Date Mailed: 05/12/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/26/2023.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sstephanos/

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/756,802	06/02/2022	Roy H. Larsen	AERA001.005APC

CONFIRMATION NO. 2930

POWER OF ATTORNEY NOTICE

OC000000057011851

20995
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

Date Mailed: 05/12/2023

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/26/2023.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sstephanos/

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/756,802	Filing Date 06/02/2022	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/12/2023	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0		x $40 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $192 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LDRC
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/ANDREW J JAMES JR/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Docket No.: A1389.70001US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Roy H. Larsen
Application No.:	17/756,802
Confirmation No.:	2930
Filed:	June 2, 2022
For:	PRODUCTION OF HIGHLY PURIFIED 212PB
Examiner:	Not Yet Assigned
Art Unit:	Not Yet Assigned

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 12, 2023 Electronic Signature for Rosa Florio: /Rosa Florio/

SECOND PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this amendment.

Remarks/Arguments begin on page 6 of this amendment.

AMENDMENTS TO THE CLAIMS

Applicant submits below a complete listing of the current claims, including marked-up claim(s) with insertions indicated by underlining and deletions indicated by strikeouts and/or double bracketing. This listing of claims replaces all prior versions, and listings, of claims in the application:

1.-38. (CANCELED)

39. (NEW) A method of generating radioisotopes, the method comprising:

exposing an interior surface of a container to a precursor isotope source by sliding a rod from a closed position in which the precursor isotope source is sealed off from the interior surface of the container to an open position in which the precursor isotope source is exposed to the interior surface of the container, wherein the precursor isotope source is disposed on the rod;

allowing sufficient time for the precursor isotope source to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes into the container; and

isolating the precursor isotope source from the container by sliding the rod from the open position to the closed position.

40. (NEW) The method of claim 39, wherein exposing the interior surface to the precursor isotope source comprises exposing the interior surface to a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the method further comprising allowing the ^{228}Th to decay into at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb).

41. (NEW) The method of claim 39, the method further comprising allowing the ^{212}Pb to deposit on the interior surface of the container.

42. (NEW) The method of claim 39, wherein isolating the precursor isotope source from the container further comprises withdrawing the precursor isotope source into a chamber having a gas tight seal.

43. (NEW) The method of claim 42, wherein withdrawing the precursor isotope source into a gas tight seal comprises sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tube.

44. (NEW) The method of claim 39, the method further comprising turning the container before exposing the interior surface to the precursor isotope.

45. (NEW) The method of claim 39, wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface.

46. (NEW) The method of claim 39, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container comprises allowing the at least one progeny isotopes to emanate into the container from the precursor isotope source through a gas permeable barrier.

47. (NEW) The method of claim 39, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source comprises allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source disposed in a sponge, a wool, a strip, or a sphere comprising at least one selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers.

48. (NEW) The method of claim 39, wherein allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours.

49. (NEW) The method of claim 39, the method further comprising changing an orientation of the container before exposing the interior surface to the precursor isotope.

50. (NEW) A system for generating radioisotopes, the system comprising:

a precursor isotope source disposed on a rod, the rod configured to slide between an open position in which the precursor isotope is exposed to an interior surface of a container to allow the precursor isotope source to decay into one or more progeny isotopes emanated into the container, and a closed position in which the precursor isotope source is sealed off from the container to isolate the precursor isotope source from the interior surface.

51. (NEW) The system of claim 50, wherein the precursor isotope source comprises a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the one or more progeny isotopes comprising at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb).

52. (NEW) The system of claim 50, wherein, in the closed position, the rod forms a gas tight seal with a tube in which the rod slides to isolate the precursor isotope source from the interior surface.

53. (NEW) The system of claim 52, wherein the rod includes at least one O-ring to form the gas tight seal with the tube in the closed position.

54. (NEW) The system of claim 50, wherein the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface.

55. (NEW) The system of claim 50, wherein the precursor isotope source is encapsulated in a gas permeable barrier.

56. (NEW) The system of claim 50, wherein the precursor isotope source is disposed on a sponge, a wool, a strip, or a sphere comprising at least one material selected from the list consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers.

57. (NEW) The system of claim 50, further comprising the container, wherein the interior surface of the container is configured to allow the ^{212}Pb to deposit on the interior surface.

58. (NEW) The system of claim 50, wherein the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours.

REMARKS

Claims 1-38 are pending in this application. By this amendment, Applicant is canceling claims 1-38 without prejudice or disclaimer. New claims 39-58 have been added. As a result, claims 39-58 are pending for examination with claims 39 and 50 being independent claims. No new matter has been added.

The pending application is believed to be in condition for substantive examination.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825, under Order No. A1389.70001US00 from which the undersigned is authorized to draw.

Dated: May 12, 2023

Respectfully submitted,

Electronic signature: /Jeffrey C. Harrigan/
Jeffrey C. Harrigan
Registration No.: 79,725
John S. Harmon, PhD, PE
Registration No.: 67,131
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/756,802-Conf. #2930
Filing Date	June 2, 2022
First Named Inventor	Roy H. Larsen
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	A1389.70001US00

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jeffrey C. Harrigan/		
Printed name	Jeffrey C. Harrigan		
Date	May 12, 2023	Reg. No.	79,725

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 12, 2023 Electronic Signature for Rosa Florio: /Rosa Florio/

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**05/12/2023 11:18:41 AM ET**	**A1389.70001US00**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Rosa Florio
PATENT CENTER #	62080450	FILING DATE	06/02/2022
CUSTOMER #	23628	FIRST NAMED INVENTOR	Roy H. Larsen
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Harrigan

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
A138970001US00-PAMN-JCH.pdf		6	-	35 KB
A138970001US00-PAMN-JCH-A.PE.pdf	(1-1)	1	Preliminary Amendment	24 KB
A138970001US00-PAMN-JCH-CLM.pdf	(2-5)	4	Claims	28 KB
A138970001US00-PAMN-JCH-REM.pdf	(6-6)	1	Applicant Arguments/Remarks Made in an Amendment	23 KB
A138970001US00-TRN-		1	Miscellaneous Incoming Letter	25 KB

JCH.pdf

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
A138970001US00-PAMN-JCH.pdf	C9FA1B53C242F96E5627F3444693345A41E0D187B3E54072CF542997BCE6FC649DCC64E78A0501841C176BBC2D6E4BAC3E81547B3743FA6F7C3243B78CF81D51
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A138970001US00-PAMN-JCH-CLM.pdf	28D2BAED98D054AC9C26909603A6438B485D0757B6990452445AC033BBD4039DFF5A447A64CA5689D236FFAC635FB8D94C4B88A2726CFBC0F2483DC52C934B81
A138970001US00-PAMN-JCH-REM.pdf	5F5F5A1EA08B37BFEA1B4087E90C31FA0D538F049CE3C303DB92528477A9AB3F5059CC2DA46BDDC5FF5D54DEDD3CDB4A20638F23156F743896F2052B7226ED94
A138970001US00-TRN-JCH.pdf	BAE020E31B4574DA1E6186E04ED1EF6F8C15D10803BE207D4365AA336AD341151027BAC1BC21D1F3358714C6518EBBC29BBE30AD1B5E15E187B270D3FD71981C

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an

international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/756,802-Conf. #2930
Filing Date	June 2, 2022
First Named Inventor	Roy H. Larsen
Art Unit	3646
Examiner Name	J. Kil
Attorney Docket Number	A1389.70001US00

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53

- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
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  - [ ] Landscape Table on CD

- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Form PTO-1449

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jeffrey C. Harrigan/		
Printed name	Jeffrey C. Harrigan		
Date	June 20, 2024	Reg. No.	79,725

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: June 20, 2024 Electronic Signature for Timothy Peng: /Timothy Peng/

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: 17/756,802	ATTY. DOCKET NO.: A1389.70001US00
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: June 2, 2022	CONFIRMATION NO.: 2930
	FIRST NAMED INVENTOR: Roy H. Larsen	
Sheet 1 of 1	GROUP ART UNIT: 3646	EXAMINER: J. Kil

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
		3,453,196		Sporek	07-01-1969
		7,476,370	B2	Mitsugashira et al.	01-13-2009
		2006-0022127	A1	Zyuzin	02-02-2006

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER:	DATE CONSIDERED:

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**06/20/2024 09:55:05 AM Z ET**	**A1389.70001US00**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Timothy Peng
PATENT CENTER #	66039325	FILING DATE	06/02/2022
CUSTOMER #	23628	FIRST NAMED INVENTOR	Roy H. Larsen
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Harrigan

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
A138970001US00-IDS1449-JCH.pdf	1	Information Disclosure Statement (IDS) Form (SB08)	21 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
A138970001US00-TRN-JCH.pdf	1	Miscellaneous Incoming Letter	26 KB
A138970001US00-IDSBODY-JCH.pdf	3	Letter specifying the conditions for filing under 37 CFR 1.97	32 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
A138970001US00-IDS1449-JCH.pdf	886AB1AD63160369E94CB298E97DF9355F6912576B99A6552505EFF68C4FED58CC1309657199F1859438C614EAEDB1726B851E05AB204275CBE290118F4258BD
A138970001US00-TRN-JCH.pdf	8522D7AF49CC05393B55767BC17D520627BC99D32C30B6145DCE6701453A0222C9CA989A2C46CEF2EBF80CE0720580F9A59A7481648923E562400139332D7782
A138970001US00-IDSBODY-JCH.pdf	8F1B81A4EC3A01EDAD7B464DCDFB13278119BC5E8F04E83489393E82E03D45C6B6D7397DD466E9EBD82A07048BFF9B2F7D7269D435A64809A4BD9B6A5C9341EC

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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DOCKET NO.: A1389.70001US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Roy H. Larsen
Application No.:	17/756,802
Confirmation No.:	2930
Filed:	June 2, 2022
For:	PRODUCTION OF HIGHLY PURIFIED 212PB
Examiner:	J. Kil
Art Unit:	3646

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: June 20, 2024 Electronic Signature for Timothy Peng: /Timothy Peng/

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Commissioner:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed before the mailing of a first Office Action on the merits.

No fee or certification is required.

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

The undersigned hereby makes the following additional information of record in the above-identified application.

The undersigned would like to bring to the Examiner's attention the following co-pending applications that may contain subject matter related to this application:

Serial No.	Filing Date	Inventor(s)	Docket No.
*18/680,372	05-31-2024	Larsen	A1389.70001US01
*18/680,605	05-31-2024	Larsen	A1389.70001US02

*A copy of this reference is not provided as the Office has waived the requirement under 37 C.F.R. § 1.98(a)(2)(iii) for submitting a copy of a cited U.S. patent application if it is scanned to the Image File Wrapper system and is available on Patent Center.

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;

3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102, or an admission by Applicant as prior art.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. A1389.70001US00 from which the undersigned is authorized to draw.

Respectfully submitted,

Electronic signature: /Jeffrey C. Harrigan/
Jeffrey C. Harrigan
Registration No.: 79,725
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Docket No.: A1389.70001US00
Date: June 20, 2024

Notice of References Cited	Application/Control No. 17/756,802	Applicant(s)/Patent Under Reexamination Larsen, Roy H.	
	Examiner SEAN M LUCK	Art Unit 2881	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-10434198-B2	2019-10-08	Larsen; Roy Hartvig	A61K51/02	1/1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/756,802	Larsen, Roy H.
	Examiner	Art Unit
	SEAN M LUCK	2881

CPC - Searched*		
Symbol	Date	Examiner
G21G1/0005	07/25/2024	SL
G21F5/015,018	07/25/2024	SL

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Cpc/text/inv/npl/for/applicant/AI/citations/backward-forward/family interference search. See attachment(s) for details.	07/25/2024	SL

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
G21G1/0005		07/25/2024	SL
G21F5/ 015,018		07/25/2024	SL

/SEAN M LUCK/ Examiner, Art Unit 2881	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/756,802	Larsen, Roy H.
	Examiner	**Art Unit**
	SEAN M LUCK	2881

CPC						
Symbol					**Type**	**Version**
G21G	/	1	/	0005	F	2013-01-01
G21F	/	5	/	015	I	2013-01-01
G21F	/	5	/	018	I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	20	
/SEAN M LUCK/ Examiner, Art Unit 2881	25 July 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	39	4

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/756,802	Larsen, Roy H.
	Examiner	**Art Unit**
	SEAN M LUCK	2881

INTERNATIONAL CLASSIFICATION				
CLAIMED				
G21G	/	1	/	00
G21F	/	5	/	015
G21F	/	5	/	018

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 20	
/SEAN M LUCK/ Examiner, Art Unit 2881 (Primary Examiner) 25 July 2024 (Date)	O.G. Print Claim(s) 39	O.G. Print Figure 4

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/756,802	Larsen, Roy H.
	Examiner	**Art Unit**
	SEAN M LUCK	2881

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19		28		37	8	46	17	55		
	2		11		20		29		38	9	47	18	56		
	3		12		21		30	1	39	10	48	19	57		
	4		13		22		31	2	40	11	49	20	58		
	5		14		23		32	3	41	12	50				
	6		15		24		33	4	42	13	51				
	7		16		25		34	5	43	14	52				
	8		17		26		35	6	44	15	53				
	9		18		27		36	7	45	16	54				

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 20	
/SEAN M LUCK/ Examiner, Art Unit 2881 (Primary Examiner)	25 July 2024 (Date)	O.G. Print Claim(s) 39	O.G. Print Figure 4

Bibliographic Data

Application No: 17/756,802

Foreign Priority claimed: (•) Yes ( ) No

35 USC 119 (a-d) conditions met: [✓] Yes [ ] No [ ] Met After Allowance

Verified and Acknowledged: /SEAN M LUCK/ Examiner's Signature [ ] Initials

Title: PRODUCTION OF HIGHLY PURIFIED 212PB

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
06/02/2022	250	2881	
RULE			

APPLICANTS

Sciencons AS, Oslo, NORWAY

INVENTORS

Roy H. Larsen, Oslo, NORWAY

CONTINUING DATA

This application is a 371 of PCT/EP2020/084701 12/04/2020

FOREIGN APPLICATIONS

EPO EP19213759.4 12/05/2019

EPO EP20172038.0 04/29/2020

IF REQUIRED, FOREIGN LICENSE GRANTED**

09/29/2022

**** SMALL ENTITY ****

STATE OR COUNTRY

NORWAY

ADDRESS

FILING FEE RECEIVED

$1,810

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	1	"17756802"	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 02:34 PM
L2	2	("20150170776" OR "20180047474").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 02:34 PM
L3	3	("3453196" "7476370" "20060022127").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 02:35 PM
L4	11	((("SCIENCONS") near3 ("AS"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 02:41 PM
L5	77	((("LARSEN") near3 ("Roy"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/07/25 02:42 PM
L6	6231	G21G1/0005.cpc. G21F5/015,018.cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO)	OR	ON	ON	2024/07/25 02:45 PM
L7	12	L4 AND L6	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO)	OR	ON	ON	2024/07/25 02:45 PM
L8	13	L5 AND L6	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2024/07/25 02:45 PM

			MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO)				
L9	13	L7 L8	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO)	OR	ON	ON	2024/07/25 02:45 PM
L10	30	(Artificial Intelligence) More like doc: US-20230014219-A1 Text: (CA-3160031-A1 OR EP-4070341-A1 OR WO-2021110950-A1 OR AU-2020398382-A1 OR IL-293575-A OR KR-20220107058-A OR JP-2023505247-A OR CN-114902350-A OR JP-WO2021110950-A5 OR MX-2022006638-A OR BR-112022010778-A2 OR US-3576998-A OR EP-0466290-A1 OR JP-H01501423-A OR CA-2046546-A1 OR JP-H05264794-A OR AU-2024203217-A1 OR CA-2631712-C OR US-20100224791-A1 OR AU-2006345883-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/25 02:46 PM
L11	1	(14/402325).APP.	(USPAT; USOCR)	OR	ON	ON	2024/07/25 03:27 PM
L12	5	("4663129" | "5038046" | "6126909" | "6787042").pn. OR ("10020086").urpn. AND (PGPB | USPT | USOC).dbnm.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 03:27 PM
L13	13	("3801818" |	(US-PGPUB; USPAT;	OR	ON	ON	2024/07/25

		"4663129").pn. OR ("5038046").urpn. AND (PGPB | USPT | USOC).dbnm.	USOCR)				03:34 PM
L14	4	("3453196").urpn. AND (PGPB | USPT | USOC).dbnm.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 03:36 PM
L15	31	(Artificial Intelligence) More like doc: US-20150170776-A1 Text: (US-20180308600-A1 OR AU-2013265268-B2 OR AU-2013265268-A2 OR US-11037690-B2 OR AU-2013265268-A1 OR EP-2854870-B1 OR WO-2013174949-A1 OR EP-2854870-A1 OR JP-2015523555-A OR JP-6392210-B2 OR DK-2854870-T3 OR FR-2990956-A1 OR TR-201811310-T4 OR ES-2683398-T3 OR US-10020086-B2 OR US-10861615-B2 OR EP-3174068-B1 OR US-20210050126-A1 OR US-20180350480-A1 OR EP-3174068-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/25 03:37 PM
L16	5	L6 AND isotope WITH rod	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 03:38 PM
L17	0	L6 AND isotope WITH precursor SAME solid	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 03:40 PM
L18	49	L6 AND isotope SAME solid	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 03:40 PM
L19	28	L6 AND (open clos$4) WITH rod	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 03:45 PM
L20	1	"17756802"	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L21	2	("20150170776" OR "20180047474").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM
L22	3	("3453196" "7476370" "20060022127").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM
L23	11	((("SCIENCONS") near3 ("AS"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM
L24	77	((("LARSEN") near3 ("Roy"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/07/25 04:07 PM
L25	6231	G21G1/0005.cpc. G21F5/015,018.cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT,	OR	ON	ON	2024/07/25 04:07 PM

			AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO)				
L26	12	L4 AND L6	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO)	OR	ON	ON	2024/07/25 04:07 PM
L27	13	L5 AND L6	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO)	OR	ON	ON	2024/07/25 04:07 PM
L28	13	L7 L8	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2024/07/25 04:07 PM

			JPO)				
L29	30	(Artificial Intelligence) More like doc: US-20230014219-A1 Text: (CA-3160031-A1 OR EP-4070341-A1 OR WO-2021110950-A1 OR AU-2020398382-A1 OR IL-293575-A OR KR-20220107058-A OR JP-2023505247-A OR CN-114902350-A OR JP-WO2021110950-A5 OR MX-2022006638-A OR BR-112022010778-A2 OR US-3576998-A OR EP-0466290-A1 OR JP-H01501423-A OR CA-2046546-A1 OR JP-H05264794-A OR AU-2024203217-A1 OR CA-2631712-C OR US-20100224791-A1 OR AU-2006345883-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/07/25 04:07 PM
L30	1	(14/402325).APP.	(USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L31	5	("4663129" | "5038046" | "6126909" | "6787042").pn. OR ("10020086").urpn. AND (PGPB | USPT | USOC).dbnm.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L32	13	("3801818" | "4663129").pn. OR ("5038046").urpn. AND (PGPB | USPT | USOC).dbnm.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L33	4	("3453196").urpn. AND (PGPB | USPT | USOC).dbnm.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L34	31	(Artificial Intelligence) More like doc: US-20150170776-A1 Text: (US-20180308600-A1 OR AU-2013265268-B2 OR AU-2013265268-A2 OR US-11037690-B2 OR AU-2013265268-A1 OR EP-2854870-B1 OR WO-2013174949-A1 OR EP-2854870-A1 OR JP-2015523555-A OR JP-6392210-B2 OR DK-	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO;	OR	ON	ON	2024/07/25 04:07 PM

		2854870-T3 OR FR-2990956-A1 OR TR-201811310-T4 OR ES-2683398-T3 OR US-10020086-B2 OR US-10861615-B2 OR EP-3174068-B1 OR US-20210050126-A1 OR US-20180350480-A1 OR EP-3174068-A1).did.	JPO; DERWENT; IBM_TDB)				
L35	5	L6 AND isotope WITH rod	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L36	0	L6 AND isotope WITH precursor SAME solid	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L37	49	L6 AND isotope SAME solid	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM
L38	28	L6 AND (open clos$4) WITH rod	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/07/25 04:07 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	973	G21G1/0005.cpc. G21F5/015,018.cpc.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 03:48 PM
N2	24	N1 AND (open clos$4) WITH rod	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 03:48 PM
N3	45	N1 AND isotope SAME solid	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 03:48 PM
N4	5	N1 AND isotope WITH rod	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 03:48 PM
N5	73	N2 N3 N4	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 03:49 PM
N6	973	G21G1/0005.cpc. G21F5/015,018.cpc.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM
N7	24	N1 AND (open clos$4) WITH rod	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM
N8	45	N1 AND isotope SAME solid	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM
N9	5	N1 AND isotope WITH rod	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM
N10	73	N2 N3 N4	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/25 04:07 PM

PTO/SB/08 Equivalent

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application No.	Unassigned
	Filing Date	Herewith
	First Named Inventor	Roy Hartvig Larsen
	Art Unit	Unassigned
(Multiple sheets used when necessary)	Examiner	Unassigned
SHEET 1 OF 1	Attorney Docket No.	AERA001.005APC

U.S. PATENT DOCUMENTS					
Examiner Initials	Cite No.	Document Number *Number - Kind Code (if known)* Example: 1,234,567 B1	Publication Date MM-DD-YYYY	Name	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear
	1	2015/0170776 A1	06-18-2015	TORGUE, Julien et al.	
	2	2018/0047474 A1	02-15-2018	O'HARA, Matthew J.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials	Cite No.	Foreign Patent Document *Country Code-Number-Kind Code* Example: JP 1234567 A1	Publication Date MM-DD-YYYY	Name	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	**T[1]**
	3	EP 0466290 A1	01-15-1992	Brunswick Corporation		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	**T[1]**
	4	International Search Report for PCT/EP2020/084701 dated February 17, 2021	

55722753/dar

Examiner Signature	/SEAN M LUCK/	Date Considered	07/25/2024

***Examiner:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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T[1] - Place a check mark in this area when an English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.L/

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 17/756,802	ATTY. DOCKET NO.: A1389.70001US00
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: June 2, 2022	CONFIRMATION NO.: 2930
				FIRST NAMED INVENTOR: Roy H. Larsen	
Sheet	1	of	1	GROUP ART UNIT: 3646	EXAMINER: J. Kil

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
		3,453,196		Sporek	07-01-1969
		7,476,370	B2	Mitsugashira et al.	01-13-2009
		2006-0022127	A1	Zyuzin	02-02-2006

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER:	DATE CONSIDERED:
/SEAN M LUCK/	07/25/2024

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.L/

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NOTICE OF ALLOWANCE AND FEE(S) DUE

23628 7590 08/06/2024

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
LUCK, SEAN M	
ART UNIT	PAPER NUMBER
2881	

DATE MAILED: 08/06/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00	2930

TITLE OF INVENTION: PRODUCTION OF HIGHLY PURIFIED 212PB

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	11/06/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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Ex. 1006 - Page 259

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23628 7590 08/06/2024
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00	2930

TITLE OF INVENTION: PRODUCTION OF HIGHLY PURIFIED 212PB

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	11/06/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
LUCK, SEAN M	2881	250-4320PD

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

AdvanCell
Ex. 1006 - Page 260

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00	2930

23628 7590 08/06/2024

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
LUCK, SEAN M	
ART UNIT	PAPER NUMBER
2881	

DATE MAILED: 08/06/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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Ex. 1006 - Page 261

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/756,802	Applicant(s) Larsen, Roy H.	
	Examiner SEAN M LUCK	Art Unit 2881	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 06/20/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 39-58 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☑ All b) ☐ Some* c) ☐ None of the:

   1. ☑ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☑ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SEAN M LUCK/
Examiner, Art Unit 2881

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Reasons for Allowance

2. The following is an examiner's statement of reasons for allowance: The prior art in general discloses the decay of solid precursor isotopes in a collection container in general, but does not provide adequate detail to address the inventive features of including said precursor on a rod that can operate the exposure in an open or closed configuration. The information provided in the prior art does not address these features, or provide a basis for a person of ordinary skill in the art to arrive at them without relying on improper hindsight reasoning or inappropriate claim interpretation.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN M LUCK whose telephone number is (571)272-6493. The examiner can normally be reached 8-5 M-F.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Kim can be reached on (571)272-2293. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SEAN M LUCK/
Examiner, Art Unit 2881

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 17/756,802	ATTY. DOCKET NO.: A1389.70001US00
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: June 2, 2022	CONFIRMATION NO.: 2930
				FIRST NAMED INVENTOR: Roy H. Larsen	
Sheet	1	of	1	GROUP ART UNIT: 2881	EXAMINER: S. M. Luck

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
		HASSFJELL, A 212Pb generator based on a 228Th source. Appl Radiat Isot. 2001 Oct;55(4):433-9. doi: 10.1016/s0969-8043(00)00372-9.	

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER:	DATE CONSIDERED:

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**08/21/2024 10:21:20 PM Z ET**	**A1389.70001US00**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Timothy Peng
PATENT CENTER #	66879824	FILING DATE	06/02/2022
CUSTOMER #	23628	FIRST NAMED INVENTOR	Roy H. Larsen
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	John Harmon

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
A138970001US00-TRN-JSH.pdf	1	Miscellaneous Incoming Letter	26 KB
A138970001US00-FEE-JSH.pdf	1	Fee Worksheet (SB06)	34 KB
A138970001US00-IDSBODY-JSH.pdf	3	Letter specifying the conditions for filing under 37 CFR 1.97	32 KB
HASSFJELL_Appl_Radiat_Isot_2001_v55_p433_NPL.pdf	7	Non Patent Literature	189 KB
A138970001US00-IDSPTA-JSH.pdf	1	Patent Term Adjustment Statement under 37 CFR 1.704(d) filed with an IDS	63 KB

A138970001US00-IDS1449-JSH.pdf	1	Information Disclosure Statement (IDS) Form (SB08)	21 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
A138970001US00-TRN-JSH.pdf	096CCFC1AF668428ADE901C292D9CE22B5D066DBCB8762F98BCD2B06DC7940DCC674402431DD43179D7B7521F17F646A295AD100D7C7A497B6FC95B52F44303B
A138970001US00-FEE-JSH.pdf	44ED30F15AF7746C480DB6E7B3181D9A4C77F188C427CA8700FCFAF28BC26035E4F61CBDEE5C090FD1CE1CFFD6781A75B7D13DDF15E2157814511506E27457B8
A138970001US00-IDSBODY-JSH.pdf	DE36ECDC39602265206C37EF0009CD2C5C89ED82E18DEF2F75391F31F074A6B1250C9AE6EB51E7A517A9FDC39BBF48A8E0BEAF8375A25777864A716FD4C89519
HASSFJELL_Appl_Radiat_Isot_2001_v55_p433_NPL.pdf	448950D8785C8C69F3B577DDCECACB65355A09FF219EB704F79F0A6561A44078A45547658C08E0446AAC1E079389207FB3B9248C8C36DEED8649AB3F9930EE28
A138970001US00-IDSPTA-JSH.pdf	EDA8F0386F7F2A09ED834D4022ACE8AC85CC5F0F59ECD1CE61F06F0E48C20C482B30DADB325D659A13D8323D2525A5C8E1DB4856DA897D211C6C1FEB28966ACD
A138970001US00-IDS1449-JSH.pdf	86EB7A14161813BE2A3792D72EC4F5CCDD1AE9454921663E8F089D287F74423C70A276BB901ED07F6FBD7E67365CF6579C64D4CBB47067160314D64C4E478973

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/756,802-Conf. #2930
Filing Date	June 2, 2022
First Named Inventor	Roy H. Larsen
Art Unit	2881
Examiner Name	S. M. Luck
Attorney Docket Number	A1389.70001US00

ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53

- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD

Remarks

- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Form PTO-1449
Form PTO/SB/133 (Patent Term Adjustment Statement)
Copy of cited reference

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/John Harmon/		
Printed name	John S. Harmon, PhD, PE		
Date	8/21/24	Reg. No.	67,131

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: 8/21/24 Electronic Signature for Timothy Peng: /Timothy Peng/

FEE TRANSMITTAL

Complete if known	
Application Number	17/756,802-Conf. #2930
Filing Date	June 2, 2022
First Named Inventor	Roy H. Larsen
Examiner Name	S. M. Luck
Art Unit	2881
Practitioner Docket No.	A1389.70001US00

[x] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)104.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [x] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[x] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[x] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[x] Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**Fees Paid ($)**
Utility	320	128*	64	700	280	140	800	320	160	
Design	220	88	44	160	64	32	640	256	128	
Plant	220	88	44	440	176	88	660	264	132	
Reissue	320	128	64	700	280	140	2,320	928	464	
Provisional	300	120	60	0	0	0	0	0	0	

* The $128 small entity status filing fee for a utility application is further reduced to $64 for a small entity applicant who files the application via Patent Center or EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	**Undiscounted Fee ($)**	**Small Entity Fee ($)**	**Micro Entity Fee ($)**
Each claim over 20 (including Reissues)	100	40	20
Each independent claim over 3 (including Reissues)	480	192	96
Multiple dependent claims	860	344	172

Total Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	- HP =	_____	x _____	=	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	- HP =	_____	x _____	=	_____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	**Fee Paid ($)**
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($168 for small entity) ($84 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		**Extra Sheets**		**Number of each additional 50 or fraction thereof**	**Fee ($)**		**Fee Paid ($)**
_____	- 100 =	_____	/50 =	_____ (round **up** to a whole number)	x _____	=	_____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $140 fee ($56 small entity) ($28 for micro entity)	
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	
Other (e.g., late filing surcharge): 2806 Submission of an Information Disclosure Statement	104.00

SUBMITTED BY

Signature	/John Harmon/	Registration No. (Attorney/Agent)	67,131	Telephone	617.646.8000
Name (Print/Type)	John S. Harmon, PhD, PE			Date	8/21/24

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: 8/21/24 Electronic Signature for Timothy Peng: /Timothy Peng/

DOCKET NO.: A1389.70001US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Roy H. Larsen
Application No.:	17/756,802
Confirmation No.:	2930
Filed:	June 2, 2022
For:	PRODUCTION OF HIGHLY PURIFIED 212PB
Examiner:	S. M. Luck
Art Unit:	2881

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: 8/21/24 Electronic Signature for Timothy Peng: /Timothy Peng/

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Commissioner:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed after the mailing date of either a Final Action under 37 C.F.R. § 1.113 or a Notice of Allowance under 37 C.F.R. § 1.311 and is being filed on or before payment of an Issue Fee.

The undersigned hereby states, as specified in 37 C.F.R. § 1.97(e), that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement.

Please charge our Credit Card in the amount of $104.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

PART II: Compliance with 37 C.F.R. § 1.704(d)

Each item of information contained in this Information Disclosure Statement

(i) was first cited in any communication from a patent office in a counterpart foreign or international application or from the United States Patent and Trademark Office, and this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty (30) days prior to the filing of the Information Disclosure Statement; or

(ii) is a communication that was issued by a patent office in a counterpart foreign or international application or by the United States Patent and Trademark Office, and this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty (30) days prior to the filing of the Information Disclosure Statement.

PART III: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

PART IV: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;

3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102, or an admission by Applicant as prior art.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. A1389.70001US00 from which the undersigned is authorized to draw.

Respectfully submitted,

Electronic signature: /John Harmon/
John S. Harmon, PhD, PE
Registration No.: 67,131
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Docket No.: A1389.70001US00
Date: 8/21/24

Doc Code: PTA.IDS
Document Description: Patent Term Adjustment Stmt Under 37 CFR 1.704(d)

PTO/SB/133 (02-23)

PATENT TERM ADJUSTMENT STATEMENT UNDER 37 CFR 1.704(d)		
	Application Number	17/756,802-Conf. #2930
	Filing Date	June 2, 2022
	First Named Inventor	Roy H. Larsen
	Art Unit	2881
	Examiner Name	S. M. Luck
	Practitioner Docket No.	A1389.70001US00

APPLICANT HEREBY STATES THE FOLLOWING (please review 37 CFR 1.704(d) before filing this form):

[x] Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in 37 CFR 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

AND/OR

[x] Each item of information contained in the information disclosure statement is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in 37 CFR 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

INSTRUCTIONS:

- **This form will not satisfy the requirement of 37 CFR 1.97(e).** The present statement is filed under 37 CFR 1.704(d) and will not substitute for compliance with any of the requirements of 37 CFR 1.97 and 1.98. For an information disclosure statement to comply with 37 CFR 1.97(c) or (d), the information disclosure statement must be accompanied by a statement under 37 CFR 1.97(e) notwithstanding any statement filed under 37 CFR 1.704(d).
- The present form (PTO/SB/133) should be filed concurrently with the information disclosure statement to derive benefit under 37 CFR 1.704(d).

Signature	/John Harmon/	Date	8/21/24
Typed or printed name	John S. Harmon, PhD, PE	Practitioner Registration Number	67,131

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

[ ] *Total of 1 forms are submitted.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: 8/21/24 Electronic Signature for Timothy Peng: /Timothy Peng/

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**08/21/2024 10:21:20 PM Z ET**	**A1389.70001US00**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Timothy Peng
PATENT CENTER #	66879824	AUTHORIZED BY	John Harmon
CUSTOMER #	23628	FILING DATE	06/02/2022
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Roy H. Larsen

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 8543	**E20248KM21595001**	**Timothy Peng**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
232825	**37 CFR 1.17 (Patent application and reexamination processing fees)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
			TOTAL AMOUNT:	**$104.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: 17/756,802	ATTY. DOCKET NO.: A1389.70001US00
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: June 2, 2022	CONFIRMATION NO.: 2930
	FIRST NAMED INVENTOR: Roy H. Larsen	
Sheet 1 of 1	GROUP ART UNIT: 2881	EXAMINER: S. M. Luck

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
		HASSFJELL, A 212Pb generator based on a 228Th source. Appl Radiat Isot. 2001 Oct;55(4):433-9. doi: 10.1016/s0969-8043(00)00372-9.	

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER:	DATE CONSIDERED:
/SEAN M LUCK/	08/27/2024

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.M.L/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00	2930

23628 7590 08/29/2024
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
LUCK, SEAN M	

ART UNIT	PAPER NUMBER
2881	

NOTIFICATION DATE	DELIVERY MODE
08/29/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Corrected ***Notice of Allowability***	**Application No.** 17/756,802	**Applicant(s)** Larsen, Roy H.	
	Examiner SEAN M LUCK	**Art Unit** 2881	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 08/21/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 39-58 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☑ All b) ☐ Some* c) ☐ None of the:

   1. ☑ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SEAN M LUCK/
Examiner, Art Unit 2881

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Reasons for Allowance

2. The following is an examiner's statement of reasons for allowance: The prior art in general discloses the decay of solid precursor isotopes in a collection container in general, but does not provide adequate detail to address the inventive features of including said precursor on a rod that can operate the exposure in an open or closed configuration. The information provided in the prior art does not address these features, or provide a basis for a person of ordinary skill in the art to arrive at them without relying on improper hindsight reasoning or inappropriate claim interpretation.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN M LUCK whose telephone number is (571)272-6493. The examiner can normally be reached 8-5 M-F.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Kim can be reached on (571)272-2293. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SEAN M LUCK/
Examiner, Art Unit 2881

UNITED STATES
PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**09/06/2024 07:40:40 PM Z ET**	**A1389.70001US00**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Eileen MacKenzie
PATENT CENTER #	67082924	FILING DATE	06/02/2022
CUSTOMER #	23628	FIRST NAMED INVENTOR	Roy H. Larsen
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	John Harmon

Documents

TOTAL DOCUMENTS: 6

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
A138970001US00-312AMN-JSH.pdf		6	-	42 KB
A138970001US00-312AMN-JSH-A.NA.pdf	(1-1)	1	Amendment after Notice of Allowance (Rule 312)	25 KB
A138970001US00-312AMN-JSH-CLM.pdf	(2-5)	4	Claims	33 KB
A138970001US00-312AMN-JSH-REM.pdf	(6-6)	1	Applicant Arguments/Remarks Made in an Amendment	25 KB
A138970001US00-CSRA-JSH.pdf		2	Post Allowance Communication - Incoming	28 KB
A138970001US00-TRN-		1	Miscellaneous Incoming Letter	26 KB

JSH.pdf			
A138970001US00-ISSFEE-JSH.pdf	1	Issue Fee Payment (PTO-85B)	38 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
A138970001US00-312AMN-JSH.pdf	FADACB07D828D5DC0DEB5D71D65F0960AA450F4D610FE5C C9E9C869E3372B4AF9A195ED965575EA709E30FF122A5F74B ECCA8DF9DAC8E04215F7A15337866A53
A138970001US00-312AMN-JSH-A.NA.pdf	191495CECB05582427D8294338B2E064D09354EEB3B9C54C6 2C61182936A5A76ED93B7E7C73BD9A58F74BAC6AF1C1E2C5 ED4895FEE64BCFEBCA443866DBB5EF7
A138970001US00-312AMN-JSH-CLM.pdf	7776115AFD40C530270F80E62BE5781B7312B182CE441AA076 8BB5F0A12C046F40658ECB17F098F054374E72620F66F09A2B EFEEA3F565DE3E029E8FA4E65892
A138970001US00-312AMN-JSH-REM.pdf	143A2D9264DE641F0EAD66D0E1DE996FF587BE98116352FDF 4A1D1D9A960CE2CF8A3B9FB6FA44D17CA653D2840BEA2A48 42552D1485E532849919435EBB923E7
A138970001US00-CSRA-JSH.pdf	5F3BCD9F315A8DE3CF1A4A6723D07F442940BD905975C12F1 AB63BC53CC16FC2D10C50FBF1561B1714F9E413999135351B 87DFBC2A5346BAC1E7B9E6AF14C58F
A138970001US00-TRN-JSH.pdf	B4CA6C948EEB7B596E258FC7C517C3EFB570466C4A7E170C 08ABBFE01BAC72B3684AB81B3A0A3965B66ACE6ABF2A1580 9DCE070E1036DDEE6097D2D77A6395AE
A138970001US00-ISSFEE-JSH.pdf	7397DBE21F1A253262AEF190E8D5B941D8EE0FB68C7F9032A C734E9226F80758639913BF7C923C28219C0559D28AB02AA12 294CC1C2A8E611C16CEB685A3A870

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/756,802	**09/06/2024 07:40:40 PM Z ET**	**A1389.70001US00**

Title of Invention

PRODUCTION OF HIGHLY PURIFIED 212PB

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	2930	FILED BY	Eileen MacKenzie
PATENT CENTER #	67082924	AUTHORIZED BY	John Harmon
CUSTOMER #	23628	FILING DATE	06/02/2022
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Roy H. Larsen

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 8626	**E202496J41248700**	**Eileen MacKenzie**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	**$480.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted via the USPTO electronic filing system or by facsimile to (571) 273-2885, on the date below.

Eileen M. MacKenzie	(Typed or printed name)
/Eileen M. MacKenzie/	(Signature)
September 6, 2024	(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00	2930

TITLE OF INVENTION: PRODUCTION OF HIGHLY PURIFIED 212PB

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480.00			$480.00	11/06/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
S. M. Luck	2881	

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Wolf, Greenfield & Sacks, P.C.
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Sciencons AS

(B) RESIDENCE: (CITY and STATE or COUNTRY): Oslo, Norway

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees Submitted: [X] Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

[X] Electronic Payment via Patent Center or EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

[X] The Director is hereby authorized to charge ~~the required fee(s),~~ any deficiency, or credit any overpayment to Deposit Account No. 23/2825

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature: /John Harmon/ Date: 9/6/24

Typed or printed name: John S. Harmon, PhD, PE Registration No.: 67,131

Docket No.: A1389.70001US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Roy H. Larsen
Application No.:	17/756,802
Confirmation No.:	2930
Filed:	June 2, 2022
For:	PRODUCTION OF HIGHLY PURIFIED 212PB
Examiner:	S. M. Luck
Art Unit:	2881

Certificate of Electronic Filing under 37 C.F.R. § 1.8
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 6, 2024 Electronic Signature for Eileen M. MacKenzie: / Eileen M. MacKenzie /

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

INTRODUCTORY COMMENTS

Prior to issuance of the patent, applicant respectfully requests entry of this amendment under 37 C.F.R. § 1.312 for the above-captioned patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this amendment.

Remarks/Arguments begin on page 6 of this amendment.

AMENDMENTS TO THE CLAIMS

Applicant submits below a complete listing of the current claims, including marked-up claim(s) with insertions indicated by underlining and deletions indicated by strikeouts and/or double bracketing. This listing of claims replaces all prior versions, and listings, of claims in the application:

39. (Previously presented) A method of generating radioisotopes, the method comprising:

exposing an interior surface of a container to a precursor isotope source by sliding a rod from a closed position in which the precursor isotope source is sealed off from the interior surface of the container to an open position in which the precursor isotope source is exposed to the interior surface of the container, wherein the precursor isotope source is disposed on the rod;

allowing sufficient time for the precursor isotope source to decay into one or more progeny isotopes and to emanate the one or more progeny isotopes into the container; and

isolating the precursor isotope source from the container by sliding the rod from the open position to the closed position.

40. (Previously presented) The method of claim 39, wherein exposing the interior surface to the precursor isotope source comprises exposing the interior surface to a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the method further comprising allowing the ^{228}Th to decay into at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb).

41. (Currently amended) The method of claim [[39]] 40, the method further comprising allowing the ^{212}Pb to deposit on the interior surface of the container.

42. (Previously presented) The method of claim 39, wherein isolating the precursor isotope source from the container further comprises withdrawing the precursor isotope source into a chamber having a gas tight seal.

43. (Previously presented) The method of claim 42, wherein withdrawing the precursor isotope source into a gas tight seal comprises sealing the rod within a tube using an O-ring to form the gas tight seal between the rod and the tube.

44. (Previously presented) The method of claim 39, the method further comprising turning the container before exposing the interior surface to the precursor isotope.

45. (Previously presented) The method of claim 39, wherein exposing the interior surface of the container to the precursor isotope source exposing the interior surface of the container to the precursor isotope source without having the precursor isotope source touch the interior surface.

46. (Previously presented) The method of claim 39, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container comprises allowing the at least one progeny isotopes to emanate into the container from the precursor isotope source through a gas permeable barrier.

47. (Previously presented) The method of claim 39, wherein allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source comprises allowing sufficient time for the at least one progeny isotopes to emanate into the container from the precursor isotope source disposed in a sponge, a wool, a strip, or a sphere comprising at least one selected from the group consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers.

48. (Previously presented) The method of claim 39, wherein allowing sufficient time for the precursor isotope source to decay comprises allowing 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours.

49. (Previously presented) The method of claim 39, the method further comprising changing an orientation of the container before exposing the interior surface to the precursor isotope.

50. (Previously presented) A system for generating radioisotopes, the system comprising:

a precursor isotope source disposed on a rod, the rod configured to slide between an open position in which the precursor isotope is exposed to an interior surface of a container to allow the precursor isotope source to decay into one or more progeny isotopes emanated into the container, and a closed position in which the precursor isotope source is sealed off from the container to isolate the precursor isotope source from the interior surface.

51. (Previously presented) The system of claim 50, wherein the precursor isotope source comprises a thorium 228 isotope (^{228}Th) and/or a radium 224 isotope (^{224}Ra), the one or more progeny isotopes comprising at least one of a radon 220 isotope (^{220}Rn) and a lead 212 isotope (^{212}Pb).

52. (Previously presented) The system of claim 50, wherein, in the closed position, the rod forms a gas tight seal with a tube in which the rod slides to isolate the precursor isotope source from the interior surface.

53. (Previously presented) The system of claim 52, wherein the rod includes at least one O-ring to form the gas tight seal with the tube in the closed position.

54. (Previously presented) The system of claim 50, wherein the rod holds the precursor isotope source without having the precursor isotope source touch the interior surface.

55. (Previously presented) The system of claim 50, wherein the precursor isotope source is encapsulated in a gas permeable barrier.

56. (Previously presented) The system of claim 50, wherein the precursor isotope source is disposed on a sponge, a wool, a strip, or a sphere comprising at least one material selected from the

list consisting of: quartz, glass, mineral, paper, plastic, metal, ceramic, natural fibers, and synthetic fibers.

57. (Currently amended) The system of claim [[50]] 51, further comprising the container, wherein the interior surface of the container is configured to allow the ^{212}Pb to deposit on the interior surface.

58. (Previously presented) The system of claim 50, wherein the precursor isotope source is configured to decay and emanate the one or more progeny isotopes into the container for 5 hours, 10 hours, 20 hours, 24 hours, 48 hours, 72 hours, or 96 hours.

REMARKS

Claims 39-58 were previously pending in this application. Claims 41 and 57 have been amended to address antecedent basis issues by changing the claim dependency. No new matter has been added.

CONCLUSION

This application is believed to be in condition for allowance. If the Examiner believes, after this amendment, the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

If this amendment is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

Applicant believes no fee is due with this Amendment. However, if a fee is due with this Amendment, please charge our Deposit Account No. 23/2825, under Docket No. A1389.70001US00 from which the undersigned is authorized to draw.

Dated: 9/6/2024

Respectfully submitted,

By /John Harmon/
Jessamine N. Lee, PhD
Registration No.: 61,674
John S. Harmon, PhD, PE
Registration No.: 67,131
Benjamin J. Walsh
Registration No.: 82,138
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	17/756,802-Conf. #2930
Filing Date	June 2, 2022
First Named Inventor	Roy H. Larsen
Art Unit	2881
Examiner Name	S. M. Luck
Attorney Docket Number	A1389.70001US00

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Part B - Issue Fee Transmittal

Comments on Statement of Reasons for Allowance

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/John Harmon/		
Printed name	John S. Harmon, PhD, PE		
Date	9/6/24	Reg. No.	67,131

Certificate of Electronic Filing under 37 C.F.R. § 1.8

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: September 6, 2024 Electronic Signature for Eileen M. MacKenzie: / Eileen M. MacKenzie /

Docket No.: A1389.70001US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Roy H. Larsen
Application No.:	17/756,802
Confirmation No.:	2930
Filed:	June 2, 2022
For:	PRODUCTION OF HIGHLY PURIFIED 212PB
Examiner:	S. M. Luck
Art Unit:	2881

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Dated: September 6, 2024 Electronic Signature for Eileen M. MacKenzie: / Eileen M. MacKenzie /

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE UNDER 37 C.F.R. § 1.104(e)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Applicant has received the Examiner's Statement of Reasons for Allowance with the August 6, 2024 Notice of Allowance and Allowability regarding the above-identified application. Entry of the Statement into the record should not be construed as any agreement with or acquiescence in the reasoning stated by the Examiner. Each of the claims stands on its own merits and is patentable because of the combination it recites and not because of the presence or absence of any one particular element.

The Examiner's Statement was not prepared by Applicant and only contains the Examiner's possible positions in one or more reasons for allowability. Thus, any interpretation with respect to the Examiner's Statement of Reasons for Allowance should not be imputed to the Applicant.

Applicant believes no fee is due with this Comments on Statement of Reasons for Allowance (37 CFR 1.104(e)). However, if a fee is due with this Comments on Statement of Reasons for Allowance (37 CFR 1.104(e)), please charge our Deposit Account No. 23/2825, under Docket No. A1389.70001US00 from which the undersigned is authorized to draw.

Dated: 9/6/24

Respectfully submitted,

By/John Harmon/
Jessamine N. Lee, PhD
Registration No.: 61,674
John S. Harmon, PhD, PE
Registration No.: 67,131
Benjamin J. Walsh
Registration No.: 82,138
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00	2930

23628 7590 09/24/2024
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
LUCK, SEAN M	

ART UNIT	PAPER NUMBER
2881	

NOTIFICATION DATE	DELIVERY MODE
09/24/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Response to Rule 312 Communication	Application No.	Applicant(s)	
	17/756,802	Larsen, Roy H.	
	Examiner	Art Unit	AIA (FITF) Status
	SEAN M LUCK	2881	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 06 September 2024 under 37 CFR 1.312 has been considered, and has been:

a) ☑ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

f) ☐ not entered because the supplemental or corrected Application Data sheet (ADS)

☐ was not accompanied by a petition to accept an unintentionally delayed claim under 37 CFR 1.55 or 27 CFR 1.78;

☐ did not identify the information being changed in accordance with 37 CFR 1.76(c)(2);

☐ was not properly signed in accordance with 37 CFR 1.76(e) (or 37 CFR 1.33(b) for applications filed prior to September 16, 2012).

/SEAN M LUCK/
Examiner, Art Unit 2881

OK TO ENTER: /S.M.L/

09/18/2024

Docket No.: A1389.70001US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Roy H. Larsen
Application No.:	17/756,802
Confirmation No.:	2930
Filed:	June 2, 2022
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Examiner:	S. M. Luck
Art Unit:	2881

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Dated: September 6, 2024 Electronic Signature for Eileen M. MacKenzie: / Eileen M. MacKenzie /

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

INTRODUCTORY COMMENTS

Prior to issuance of the patent, applicant respectfully requests entry of this amendment under 37 C.F.R. § 1.312 for the above-captioned patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this amendment.

Remarks/Arguments begin on page 6 of this amendment.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/756,802	10/22/2024	12125603	A1389.70001US00	2930

23628 7590 10/02/2024

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 335 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Roy H. Larsen, Oslo, NORWAY;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Sciencons AS, Oslo, NORWAY;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/756,802	06/02/2022	Roy H. Larsen	A1389.70001US00	2930

23628 7590 10/22/2024
WOLF GREENFIELD & SACKS, P.C.
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EXAMINER	
LUCK, SEAN M	

ART UNIT	PAPER NUMBER
2881	

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Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
17/756,802	22-Oct-2024	12125603

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants