Journal of Analytical Atomic Spectrometry

JAAS

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| Journal: | *Journal of Analytical Atomic Spectrometry* |
| Manuscript ID | JA-ART-11-2021-000393.R2 |
| Article Type: | Paper |
| Date Submitted by the Author: | 11-May-2022 |
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# Quadrupole and Multi-Collector ICP-MS Analysis of $^{226}$Ra in Brain from a Radium Dial Painter

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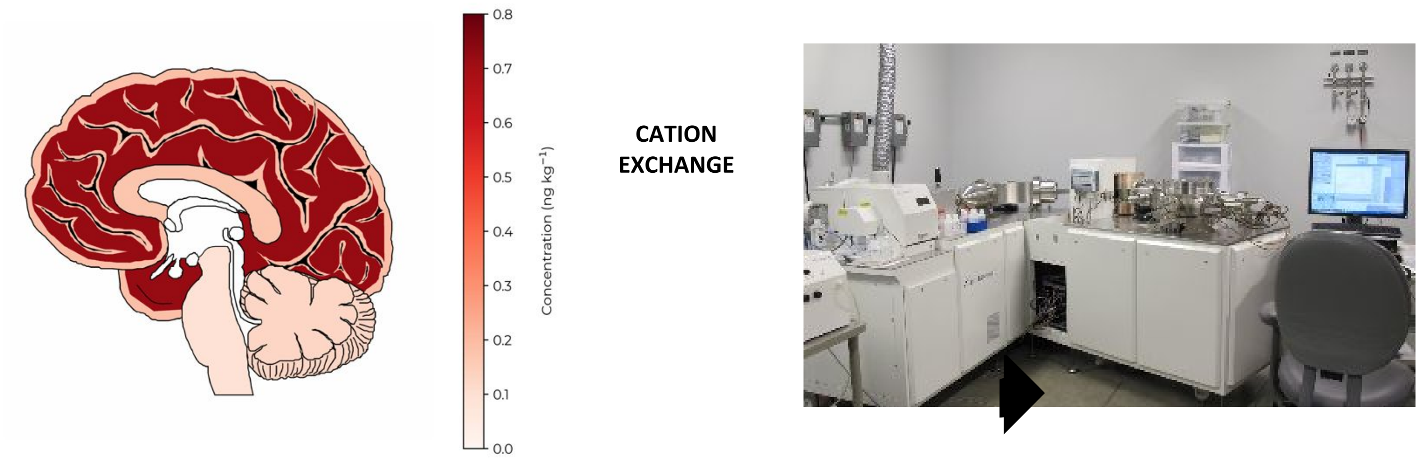



**Abstract**

Two ICP-MS methods were developed to measure the radiotoxic isotope $^{226}$Ra in brain tissues from a radium dial painter worker. The first method was a direct analysis of acid digested samples using quadrupole ICP-MS. The instrumental LOD of $^{226}$Ra was 0.1 ng/kg. Polyatomic interferences at m/z 226 were investigated and Pb was identified form a polyatomic interferent in an in-house sample prepared from bovine brain, with a 226/208 formation ratio of $4 \times 10^{-8}$. The quadrupole ICP-MS method was also used to measure levels of beryllium, strontium, and

uranium. A second method was developed that included cation-exchange chromatography to separate $^{226}Ra$ followed by analysis with sector field MC-ICP-MS. The instrumental LOD for the cation exchange method with MC-ICP-MS detection was 0.5 pg/kg (19 mBq/kg). The measured concentrations of $^{226}Ra$ in different brain regions ranged from 0.09 – 0.72 ng/kg (3.3 – 27 Bq/kg) and radium was non-uniformly distributed in the brain.

## Introduction

Radium is a radioactive alkaline earth metal produced through the natural radioactive decay chains. Among the radium isotopes, $^{226}Ra$ has the longest half-life of 1600 ± 7 years.[1] The $^{226}Ra$ decay chain produces 4 alpha particles and 4 beta particles before terminating at $^{206}Pb$. Internal exposure to $^{226}Ra$ and its progeny are a human health concern due to effects of high linear energy transfer (LET) ionizing radiation.[2] Human exposure to radium occurs through consumption of food and water. The concentration of $^{226}Ra$ in natural waters ranges from 0.14 – 0.55 pg/L ( 0.5 – 20 mBq/L).[3] Combustion of coal releases $^{226}Ra$ with concentrations in fly ash ranging from 1.21 – 65.6 ng/kg (44.3 – 2400 Bq/kg).[4] Plants uptake $^{226}Ra$ through root and foliar processes.[3] Animals are exposed through ingestion of food and water.[3]

The health effects of $^{226}Ra$ exposure have been studied using data from the United States Radium Dial Workers cohort.[5] The watch dial painters, who were predominantly women, applied a luminescent mixture of $^{226}RaSO_4$ and ZnS onto watch dials and other instruments. Prior to 1926, it was common practice for the dial painters to "tip" or "point" the paintbrush using their lips leading to ingestion of radium. [6] The ingested $^{226}Ra$ primarily accumulated in bone and the watch dial painters had an increased risk of developing osteomyelitis, osteosarcomas, and head carcinomas of the mastoid and paranasal sinus.[7,8] The watch dial painter's studies were used in the development of a radium biokinetic model published by the International Commission on Radiological Protection (ICRP).[9]

$^{223}RaCl_2$ is currently being used for the treatment of osteosarcoma. In one case study, a patient treated for osteosarcoma with $^{223}RaCl_2$ was observed to have shrunken metastasis in the cerebellum brain region.[10] This observation suggests that radium could be transported across the intact blood brain barrier (BBB), potentially by calcium transporters.[11–14] Although in this case it is unclear if the BBB integrity was compromised by cerebellar metastases or radiation damage. Adverse neurological effects associated with exposure to $^{226}Ra$ and other high LET emitters are currently under investigation in the Million Person Study (MPS).[15] The neurological effects of high-LET radiation is also of interest for estimating risk associated with exposure to high-LET galactic cosmic radiation (GCR) during manned space flights.[16,17] Direct measurement of $^{226}Ra$ in neurological tissue samples from the watch dial painter cohort would provide additional evidence that radium can cross the blood brain barrier and provide data for development of a radium biokinetic model with a brain compartment.

$^{226}Ra$ can be measured by radiometric and mass spectrometry methods.[18] Radiometric techniques include alpha spectroscopy, liquid scintillation counting, and emanation counting. Alpha spectroscopy requires a thin, plated source of $^{226}Ra$ to minimize self-absorption and 48-hour count times. An alpha spectroscopy method that used cation exchange chromatography with selective complex formation followed by electrodeposition reported detection $^{226}Ra$ detection limits of 0.014 pg/L (0.5 mBq/L) in urine samples and 0.014 pg (mBq) in bone biopsy samples.[19,20] Many studies have reported low radium recoveries if radium separation from other alkaline-earth metals was incomplete or the extractant ligands were not removed.[20–22]

Another radiometric method that can be used to measure the alpha emissions of $^{226}$Ra and its decay products $^{222}$Rn, $^{218}$Po, and $^{214}$Po is liquid scintillation counting (LSC). The detection limits for LSC are 0.008 – 0.04 pg/L (0.3 – 1.4 mBq/L). [23–27] A limitation of this method is the 3-week delay time necessary to allow for ingrowth of the $^{226}$Ra decay products.[26] Historically, $^{226}$Ra has been measured using the emanation method which was developed in the 1920's and first used to measure $^{226}$Ra in blood, serum, and autopsy bone samples in the United States Radium Dial Workers cohort studies.[28,29] In this method $^{226}$Ra is co-precipitated with barium sulfate and the $^{222}$Rn daughter is allowed to equilibrate over 5 days, captured, and then counted using a scintillation cell. Detection limits for the emanation method range from 0.02 – 0.08 pCi/L (0.1 - 3 mBq/kg).[30]

Inductively coupled plasma mass spectrometry (ICP-MS) has emerged as a sensitive method to measure $^{226}$Ra in surface and drinking water, sediments, environmental samples, and urine.[31–34] Polyatomic interferences formed from $^{209}Bi^{17}O^+$, $^{209}Bi^{16}O^1H^+$, $^{199}Hg^{27}Al^+$, $^{202}Hg^{24}Mg^+$, $^{208}Pb^{18}O^+$, $^{208}Pb^{17}O^1H^+$, $^{208}Pb^{16}O^1H_2^+$, $^{194}Pt^{16}O_2^+$, $^{86}Sr^{140}Ce^+$, $^{87}Sr^{139}La^+$, $^{88}Sr^{138}Ba^+$, $^{203}Tl^{23}Na^+$, $^{186}W^{40}Ar^+$, and $^{186}W^{40}Ca^+$ potentially interfere with direct measurement of $^{226}$Ra.[35] ICP-MS analysis with He collision gas has been demonstrated to minimize polyatomic interferences in environmental samples.[35] Polyatomic interferences can also be reduced by separating $^{226}$Ra from the matrix and isobaric interferences cation exchange chromatography.[36–40] A study by Dalencourt *et al*. reported an instrumental LOD of 0.530 pg/L

(19 mBq/kg) for $^{226}$Ra in environmental samples. [31] By introducing cation exchange separation for removing interferences, the authors reported a method LOD of 0.01 pg/L (0.37 mBq/kg).[31]

An advantage of ICP-MS is its multi-element capability. Beryllium and uranium exposures occur at nuclear laboratories working on weapons production.[41,42] Beryllium workers are at risk for developing berylliosis.[43] The radionuclide $^{90}$Sr is a fission product that is released during nuclear accidents.[44] Exposure to $^{90}$Sr has been a concern at Chernobyl and Fukushima.[45] Strontium is expected to have similar chemistry to radium since they are both alkaline earth metals.

The objective of this work was to develop a mass spectrometry method to measure $^{226}$Ra in human brain tissue samples. We evaluated two ICP-MS methods used to measure $^{226}$Ra in brain tissue samples from a watch dial painter. Preliminary results examining the $^{226}$Ra levels in brain measured by ICP-Q-MS were discussed by Martinez *et al.* and Boice *et al*.[46,47] The multi-element detection capabilities of ICP-MS enabled the potential for the simultaneous measurement of beryllium, strontium, and uranium.

## Experimental

### Case description

In the 1920's, this individual worked as a radium dial painter for almost 7 years and died 6 decades later at the age of 86 yr.[48] Selected tissue samples were collected at the time of the autopsy. In 1973, the $^{226}$Ra skeletal dose based on ICRP 20 was estimated at 5047 cG, a systemic deposition of $^{226}$Ra at 261.7 μg (9.683 MBq), and a total body content of $^{226}$Ra at 1.077 μg (0.03985 MBq) .[5]

**Materials, Reagents, and Instrumentation**

The water used in this study was 18 MΩ produced by a Milli-Q water purification system. Trace metal grade certified HCl and $HNO_3$ were purchased from Fischer Scientific, and L(+)-ascorbic acid was purchased from Acros Organics. The thorium standard for ICP-MS was purchased from High Purity Standards. Cation exchange column chromatography was conducted using analytical grade AG 50W-X8 (200-400 mesh) from BioRad. The $^{226}Ra$ standard reference material SRM 4976A (69.0 pg/L, 2524 mBq/L) was purchased from NIST and used to prepare spike solutions for the standard addition calibration. Spikes of beryllium, strontium, and uranium were prepared from commercial standards (High-Purity Standards). Glassware used in the dry ashing procedure was washed with 10% nitric acid prior to use. Polypropylene tubes used during the analysis were precleared using dilute nitric acid.

Two instruments were used in this study. A Perkin Elmer NexION 300X ICP-MS quadrupole instrument (ICP-Q-MS) and a Nu Plasma II Multi Collector (MC) ICP-MS sector field instrument. The ICP-Q-MS settings are described in Table 1 and the MC-ICP-MS instrument settings are described in Table 2. The detector block of the Nu-Plasma II was set up to analyze $^{232}Th$ on a faraday cup (L2) and $^{226}Ra$ on an ion counter (IC2).

Table 1. Instrument settings for NexION 300X ICP-Q-MS

| | |
|---|---|
| RF power, W | 1600 |
| Plasma gas, L/min | 18 |
| Carrier gas, L/min | 1.06 |
| Cones | Nickel |
| Nebulizer | Quartz |
| Spray chamber | Elemental Scientific PFA cyclonic spray chamber (7 mm baffle) |

| | |
|---|---|
| Acquisition mode | Standard mode |
| Isotopes | $^{9}$Be, $^{86}$Sr, $^{115}$In, $^{138}$Ba, $^{139}$La, $^{140}$Ce, $^{146}$Nd, $^{186}$W, $^{200}$Hg, $^{202}$Hg, $^{203}$Tl, $^{208}$Pb, $^{209}$Bi, $^{226}$Ra, $^{232}$Th, $^{238}$U |
| Integration time, ms | 500 |
| Replicates | 5 |

Table 2. Instrument settings for Nu Plasma II MC-ICP-MS

| | |
|---|---|
| RF power, W | 1300 |
| Reflected power, W | 0 |
| Neb, PSI | 33.5 |
| Auxiliary gas, L/min | 0.8 |
| Coolant, L/min | 13 |
| Cones | Nickel |
| Nebulizer | Quartz |
| Spray chamber | Nu desolvation nebulizer (DSN-100) |
| Isotopes | $^{226}$Ra, $^{232}$Th |
| Integration time, ms | 30 |
| Replicates | 25 |

**Sample Preparation**

In 1992, autopsy tissue sample collection from radium dial painters was transferred from Argonne National Laboratory to the National Radiation Biology Tissue Repository (NHRTR) at the United States Transuranium and Uranium Registries (USTUR).[5] At the NHRTR/USTUR, tissue samples were stored frozen or formalin-fixed. The weight of formalin-fixed brain tissue from this individual was 449 g. The brain was dissected into 5 regions: cerebrum white matter, cerebrum gray matter, corpus collosum, cerebellum, and brainstem. Samples were dry-ashed at 500 °C for 4 days, followed by microwave acid digestion for 20 min with reverse aqua regia at 200 °C. The samples were evaporated and brought up in 4M HCl for storage. The USTUR provided 15 mL samples from each storage solution. The 15 mL sample was subdivided into 5 mL samples that were evaporated to dryness and dissolved in 3 mL of 3% HCl with indium and thorium internal standards. Table 3 lists the starting sample masses, the storage masses, and representative final dilution factors for each tissue type. Reagent (4M HCl) and method (bovine brain tissue) blanks were prepared using the same procedure. Two subsamples of each tissue type were directly analyzed by ICP-Q-MS.

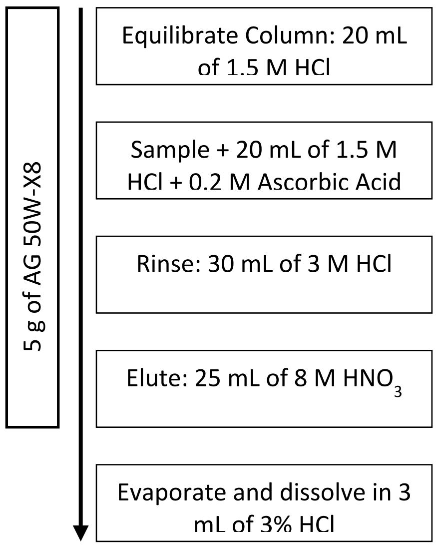
Table 3. The dissected tissue mass, storage mass, and representative dilution factors for the brain tissue samples.

| Tissue | Dissected Mass (g) | Storage Solution Mass (g) | Dilution Factor |
|---|---|---|---|
| Cerebrum White Matter | 147.71 | 262.56 | 1.07 |
| Cerebrum Gray Matter | 164.6 | 262.74 | 0.96 |
| Corpus Collosum | 31.64 | 131.75 | 2.50 |
| Cerebellum | 87.72 | 132.2 | 0.90 |
| Brainstem | 17.33 | 132.14 | 4.57 |

**Radium Separation**

The $^{226}Ra$ in the third subsample was separated from the matrix using a cation exchange chromatography method adapted from Maxwell *et al.* [39] The sample was evaporated and the residue was redissolved in 20 mL of 1.5 M HCl and 3 mL of 1.5 M ascorbic acid. The ascorbic acid addition was present to reduce iron to $Fe^{2+}$ to minimize its retention on the column. Approximately 5 g of AG 50W-X8 resin was mixed with an equal amount of 18 MΩ $H_2O$ and packed into a column. The gravity column was equilibrated by rinsing with 20 mL of 1.5 M HCl and then the sample was added. The resin was then rinsed with 30 mL of 3 M HCl to elute the matrix and the cations Ca, Pb, and Bi.[37–39] The $^{226}Ra$ was eluted from the column with 25 mL of

8 M $HNO_3$. The $^{226}Ra$ fraction was evaporated and the residue redissolved in 3 mL of 3% HCl with 1 mg/kg thorium internal standard. The recovery was determined by spiking a method




blank with 10 pg of $^{226}Ra$.

**Figure 1.** Chemical separation procedure for $^{226}Ra$ determination in brain

**ICP-MS Measurement**

Potential polyatomic interference for $^{226}Ra$ were investigated (Table 4). For each potential interference, the primary, expected elements concentration in human brain tissue[35,49] and the corresponding level in the digestate are presented.

**Table 4.** Potential interferences investigated for $^{226}Ra$ in tissues evaluated using ICP-Q-MS.[35,49] Elements listed as N/A do not have a reported range in brain tissue.

| Primary element | Polyatomic interference | Estimated concentration (mg/kg) in |
|---|---|---|

| | | brain tissue, digestate* |
|---|---|---|
| Bi | $^{209}Bi^{17}O^+$ | Bi: 0.01, 0.011 |
| | $^{209}Bi^{16}O^1H^+$ | |
| Hg | $^{199}Hg^{27}Al^+$ | Hg: 3, 3.3 |
| | $^{202}Hg^{24}Mg^+$ | Al: 20, 22 |
| | | Mg: 100, 110 |
| Pb | $^{208}Pb^{18}O^+$ | Pb: 1.6, 1.8 |
| | $^{208}Pb^{17}O^1H^+$ | |
| | $^{208}Pb^{16}O^1H_2^+$ | |
| Pt | $^{194}Pt^{16}O_2^+$ | Pt: N/A |
| Sr | $^{86}Sr^{140}Ce^+$ | Sr: 5, 5.5 |
| | $^{87}Sr^{139}La^+$ | Ce: N/A |
| | $^{88}Sr^{138}Ba^+$ | La: 0.001, 0.0011 |
| | | Ba: 2, 2 |
| Tl | $^{203}Tl^{23}Na^+$ | Tl: <0.001, 0.001 |
| | | Na: 1,750, 1750 |
| W | $^{186}W^{40}Ar^+$ | W: N/A |
| | $^{186}W^{40}Ca^+$ | Ca: 6,000, 6,600 |

* The digestate concentration is based on a DF of 0.9, see Table 3.

The standards addition method reported by Ellison and Thompson [50] was used to quantify $^{226}Ra$, $^{9}Be$, $^{86}Sr$, and $^{238}U$. The concentration in the unknown (T) is determined using the following equation:

$$T = C\frac{r_T}{r_{T+C} - r_T}$$

where C is the concentration in the spike, $r_T$ is the response of unknown concentration, and $r_{T+C}$ is the response of unknown of concentration + spike. Each 3 mL sample was analyzed, consuming ~1.2 mL of solution, and then spiked with the standard solution to approximately five times the signal in the original sample. The samples were bracketed by instrument blanks to minimize carryover. The instrument LOD for ICP-Q-MS was determined from analysis of 35 instrument blanks and calculated as 3 times the standard deviation of the concentration in the instrumental blank. The instrument LOD for the MC-ICP-MS was measured using 20 replicate acid blanks and calculated as 3 times the standard deviation of the concentration in the instrumental blank.

**Statistical Analysis**

The uncertainty in the concentration was determined using the guidelines for uncertainty in measurement (GUM) using the GUM workbench (Metrodata GmbH version 2.4) and reported at the 1σ level (68% confidence level, coverage factor k=1). The association of Be and Sr with $^{226}Ra$ was investigated using Spearman's rank-order correlation (Prism GraphPad).

**Results and discussion**

None of the concentrations tested in Table 4 leads to a significant measurable signal at *m/z* of 226 using an ICP-Q-MS. The two ICP-MS method for $^{226}Ra$ determination in brain tissue appear to be free of polyatomic interference. The brain tissue digestate samples were subsequently analyzed in STD mode without any collision gas to maximize the instrument sensitivity.

The ICP-Q-MS instrument produced a signal of 62 ± 7 cps for a 1000 pg/kg $^{226}$Ra solution. The subsequent instrument blank had a measured signal of ~ 0.6 cps at *m/z* = 226 and a signal to blank ratio of 100. The instrument blank demonstrated that the washout conditions were acceptable. The instrumental LOD for $^{226}$Ra was 80 pg/kg (2930 mBq/kg). The instrumental LODs for $^{9}$Be, $^{86}$Sr, and $^{238}$U were 30 ng/kg, 200 ng/kg, and 200 ng/kg, respectively. The method blanks prepared from the bovine brain had an apparent $^{226}$Ra concentration of 300 pg/kg ($1.1 \times 10^5$ mBq/kg). Investigation found that the bovine brain contained 2500 times more lead than the expected range in human brain. Potential lead-based polyatomic interferences, reported in Table 3, are $^{208}Pb^{18}O^+$, $^{208}Pb^{17}O^1H^+$, and $^{208}Pb^{16}O^1H_2^+$. An acid matched, single element lead standard was prepared, and the observed 226/208 formation ratio was $4 \times 10^{-8}$. The bovine brain sample was spiked with twice the measured lead level and a corresponding increase at *m/z* = 226 was observed. Both the instrument blanks prepared onsite, and acid blanks prepared by the USTUR did not contain lead. The bovine brain sample could not be used as a method blank because of the high lead levels. Lead levels should be monitored when measuring $^{226}$Ra using ICP-MS levels. A correction based on the 226/208 formation ratio was applied to the bovine brain sample which lowered the $^{226}$Ra concentration below the instrumental LOD. It is unclear why the bovine brain contained high levels of lead.

There are several limitations to the direct solution analysis with ICP-Q-MS. In the unseparated brain samples, the signal from the thorium internal standard was suppressed 4-fold relative to the acid matched $^{226}$Ra external standard. The signal suppression is attributed to the high matrix levels of the samples, dilution factors reported in Table 3. The standard addition method is used to minimize the matrix effect; however, the signal suppression still reduced the sensitivity for $^{226}$Ra. Another consideration is that unknown polyatomic isobars could still be present in the high matrix samples. Increasing the dilution by a factor of 3-5 could potentially lead to a reduction in the matrix effect and an increase in sensitivity. Matrix reduction could also be improved through separation of $^{226}$Ra prior to ICP-Q-MS.

The $^{226}$Ra level was also measured by MC-ICP-MS following cation exchange chromatography. The separation recovery factor measured from the matrix blank spiked with 10 pg of $^{226}$Ra was 98% ± 2%. A 1000 pg/kg solution of $^{226}$Ra produced a signal of $2.5 \times 10^{-4}$ mV on the ion counter detector. The washout in the subsequent acid blank produced a $^{226}$Ra signal of $10^{-7}$ mV and a signal to blank ratio of 2500, 25 times higher than the ICP-Q-MS measurements. The instrumental LOD of $^{226}$Ra using the MC-ICP-MS was 0.5 pg/kg (19 mBq/kg). This value was 160 times lower than the direct analysis method using the ICP-Q-MS and similar to LODs reported in the literature, see Table 5. The method LOD for MC-ICP-MS analysis of $^{226}$Ra ranged from 0.5 to 2 pg/kg (0.02 – 0.07 mBq/kg) depending on the dilution factor, see Table 3.

**Table 5**. Comparison of mass spectrometric methods for $^{226}$Ra analysis.

| Author | Sample Type | Detection Method | Instrumental LOD pg/kg |
|---|---|---|---|
| This work | Brain tissue | ICP-Q-MS | 80 |
| This work | Brain tissue | MC-ICP-MS | 0.55 |
| Copia *et al.*[40] | Groundwater | SF-ICP-MS | 0.090 |

| | | | |
|---|---|---|---|
| Larivière *et al.*[51] | Well water | SF-ICP-MS | 15 |
| Benkhedda *et al.*[52] | Natural waters | ICP-MS | 3.0 |
| Tsai *et al.*[53] | Geothermal water, sediment | ICP-MS | 560 |
| Dalencourt *et al.*[31] | Environmental | ICP-MS | 0.53 |
| Yaala *et al.*[35] | Sediment | ICP-MS | 0.10 |

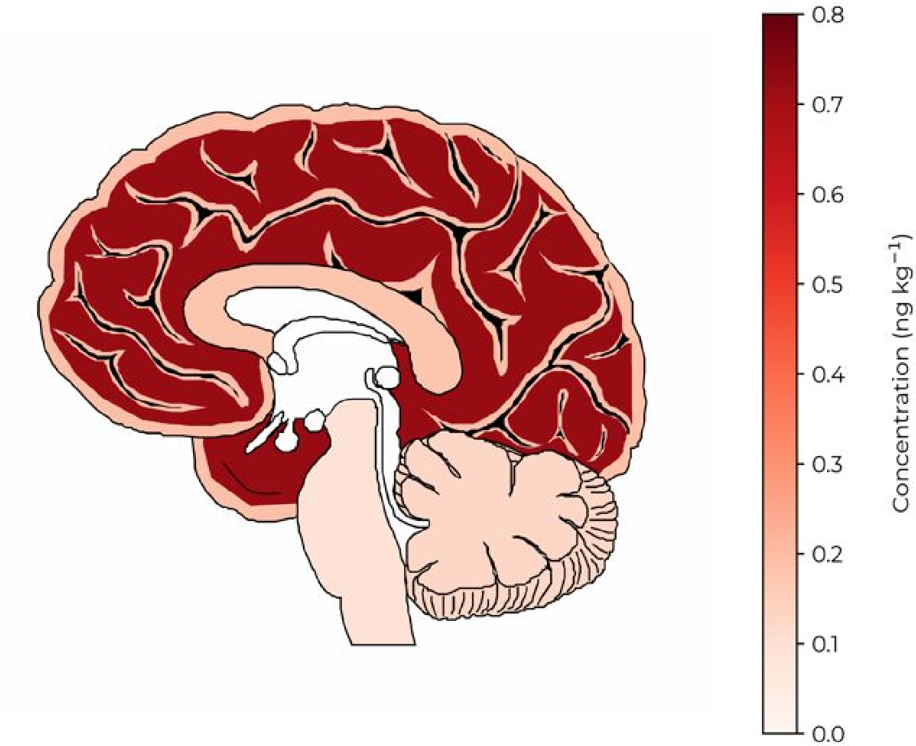
The measured tissue concentrations of $^{226}$Ra, $^{9}$Be, $^{86}$Sr, and $^{238}$U measured in the five regions of the brain by ICP-Q-MS and MC-ICP-MS are reported in Table 6. The $^{226}$Ra levels reported for ICP-Q-MS were corrected for the $^{208}$Pb based interferences. The correction accounted for less than 1% of the $^{226}$Ra level in the samples. The $^{226}$Ra results for the direct ICP-Q-MS method and the MC-ICP-MS agree within the uncertainty of the measurements. The high uncertainties for the $^{226}$Ra measurements by ICP-Q-MS measurements are due to the proximity of the $^{226}$Ra levels to the LOD. The agreement between methods suggests that polyatomic species did not significantly interfere with the direct measurement of $^{226}$Ra using the ICP-Q-MS. The improvement in sensitivity from the MC-ICP-MS method originated from increased instrument sensitivity and from separation of the $^{226}$Ra from the matrix. The sensitivity of the ICP-Q-MS method would also have been improved by removal of the matrix.

**Table 6**. Mass concentrations (above) and activity concentrations (below) with uncertainties (1 standard deviation) of $^{226}$Ra, $^{9}$Be, $^{86}$Sr, and $^{238}$U in various brain regions measured by MC-ICP-MS and ICP-Q-MS.

| Sample | MC-ICP-MS | ICP-Q-MS | | | |
|---|---|---|---|---|---|
| | $^{226}$Ra ng/kg<br>$^{226}$Ra mBq/kg | $^{226}$Ra ng/kg<br>$^{226}$Ra mBq/kg | $^{9}$Be, µg/kg | $^{86}$Sr, mg/kg | $^{238}$U, µg/kg |
| Cerebral white matter | 0.72 ± 0.04<br>26 ± 1 | 0.52 ± 0.24<br>19 ± 9 | 0.54 ± 0.04 | 0.163 ± 0.010 | 31 ± 1 |
| Cerebral gray matter | 0.187 ± 0.006<br>6.8 ± 0.2 | 0.2 ± 0.2<br>6 ± 6 | 0.73 ± 0.05 | 0.156 ± 0.006 | 44 ± 3 |
| Corpus callosum | 0.17 ± 0.01<br>6.2 ± 0.4 | <0.2<br><7 | 0.81 ± 0.06 | 0.137 ± 0.005 | 31 ± 1 |
| Cerebellum | 0.13 ± 0.03<br>4.8 ± 0.1 | 0.19 ± 0.17<br>7 ± 6 | 0.46 ± 0.04 | 0.100 ± 0.004 | 34 ± 1 |
| Brainstem | 0.090 ± 0.003<br>3.3 ± 0.1 | <0.4<br><15 | 0.50 ±0.05 | 0.115 ± 0.004 | 35 ± 1 |

The total concentration of $^{226}$Ra in the dissected fixed brain sample, 0.35 ng/kg (18 mBq/kg) was determined from a weighted average of the segments measured using the MC-ICP-MS method. The total mass of $^{226}$Ra in the 449 g brain was 0.16 ng (5700 mBq). The $^{226}$Ra mass in the brain therefore accounts for 0.014% of the total body content of $^{226}$Ra. The $^{226}$Ra levels were uniformly distributed among cerebral gray matter, corpus collosum, and cerebellum. The $^{226}$Ra concentration was elevated in cerebral white matter and reduced in the brainstem (Table 6), depicted in Figure 2.

**Figure 2.** $^{226}Ra$ concentration distribution in the human brain




A Spearman's rank order correlation was used to assess the relation between $^{226}Ra$ and $^{9}Be$ as well as $^{226}Ra$ and $^{86}Sr$. The correlation between $^{226}Ra$ and $^{9}Be$ was not significant, $r(3) = 0.50$, $p = 0.39$. The correlation between $^{226}Ra$ and $^{86}Sr$ was significant, $r(3) = 0.90$, $p = 0.037$. Because strontium is also the analogue of calcium, the correlation suggests that radium and strontium could enter the brain using the calcium transport systems. In this study, a single brain was analyzed for $^{226}Ra$. Establishment of a general $^{226}Ra$ distribution in the brain would require analysis of additional samples.

Strontium has been previously measured in human brains from individuals without a neurological disease with a range of 0.020 – 0.224 mg/kg (dry weight).[54] These results compare well with the present work which had a mean Sr concentration of 0.134 mg/kg. A study by Meehan *et al*. measured the concentration of beryllium via fluorimetric determination in various human organs finding an average of 0.08 mg/kg ash weight ($1 \times 10^{-3}$ mg/kg fresh weight) in brain.[55] The results presented in this work are on the low end of the literature value. In a study using neutron activation analysis to measure uranium in brain, the mean value was $<8 \times 10^{-3}$ mg/kg.[54] Kathren and Tolmachev examined the uranium content in brain tissue of three individuals using alpha spectrometry with the following results: $2.3 \times 10^{-4}$ mg/kg, $1.8 \times 10^{-4}$ mg/kg, and $7.7 \times 10^{-4}$ mg/kg.[56] The values measured in this study are at the high-end of the results published in literature.

One limitation of this study that the undissected brain was stored in formalin solution for years. Formalin preservation can result in contamination or leaching of the analyte from tissue.[57] In work by Gellein *et al.*, the concentration of strontium was measured in the formalin solution containing fixed human brain tissue stored over long periods of time.[58] The strontium concentration in the formalin solution increased by a factor of 59 over long term storage compared to fresh formalin solution. However, it was unclear if formalin leached strontium from the brain only or from the brain and the glass storage container. A study by Bush *et al.*, reported that fresh biological tissue stored in formalin for 12 months resulted in decreases in the tissue concentration of magnesium and manganese but not calcium.[59] It is therefore unclear from the literature if the long term storage in formalin resulted in decreased $^{226}Ra$ levels in the brain. Unfortunately, samples of the formalin storage solution were not available for this work.

**Conclusions**

The ICP-MS based method for quantification of $^{226}Ra$, along with beryllium, strontium, and uranium, in human brain was developed. The combination of analyte separation from tissue matrix and MC-ICP-MS analysis improved the sensitivity of the method by reducing matrix effects and possible isobaric interferences compared to direct ICP-Q-MS analysis. The LOD of the ICP-Q-MS was approximately 160 times higher than the LOD of the MC-ICP-MS method. The $^{226}Ra$ analysis method presented is an alternative method to radiometric methods, which require long counting times with limited sample throughput. The obtained results of $^{226}Ra$ concentrations in human brain regions could be used to support the further development of biokinetic models for radiation dose assessment to the brain after $^{226}Ra$ intake.[16] The method could be applied to analyze radium in brain tissue samples collected from other watch dial painters or in other autopsy samples. This study found that $^{226}Ra$ was uniformly distributed among cerebral gray matter, corpus collosum, and cerebellum tissue (0.19 – 0.13 ng/kg or 6.8 – 4.8 mBq/kg). The $^{226}Ra$ concentration in cerebral white matter (0.72 ng/kg or 26 mBq/kg) was elevated compared to other regions and it was mildly reduced in the brainstem (0.09 ng/kg or 3.3 mBq/kg). The concentrations of $^{226}Ra$ and strontium in brain tissues were correlated, suggesting that they are transported across the BBB using the same transporters.

**Acknowledgements**

This paper was based on research conducted under a Fellowship grant to The Curators of the University of Missouri (award #NRC-HQ-15-G-0036) from the Office of the Chief Human Capital Officer of the Nuclear Regulatory Commission. The statements, findings, conclusions, and recommendations are those of the author(s) and do not necessarily reflect the view of the Outreach and Recruitment Branch or the US Nuclear Regulatory Commission. The USTUR is funded by U.S. Department of Energy, Office of Domestic and International Health Studies (AU-13) under grant award DE-HS0000073 to College of Pharmacy and Pharmaceutical Sciences at Washington State University.

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