

**Elemental bio-imaging of thorium, uranium and plutonium
in tissues from occupationally exposed former nuclear
workers**

Journal:	<i>Analytical Chemistry</i>
Manuscript ID:	ac-2009-02650w.R1
Manuscript Type:	Article
Date Submitted by the Author:	10-Feb-2010
Complete List of Authors:	Hare, Dominic; UTS Tolmachev, Sergei; bUnited States Transuranium & Uranium Registries James, Anthony; bUnited States Transuranium & Uranium Registries Bishop, David; UTS Austin, Christine; Univerisity of Technology Sydney,, Institute for Nanoscale Technology Fryer, Fred; Agilent Technologies Doble, Philip; Univesity of Technology, Sydney, Department of Chemistry and Forensic Science



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3 **Elemental bio-imaging of thorium, uranium and plutonium in tissues from occupationally exposed**
4 **former nuclear workers**
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7 *Dominic Hare^a, Sergei Tolmachev^b, Anthony James^b, David Bishop^a, Christine Austin^a, Fred Fryer^c, and*
8 *Philip Doble^{*a}*
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11 ^a*Elemental Bio-imaging Facility, University of Technology, Sydney, Broadway, New South Wales, Australia.*

12 ^b*United States Transuranium & Uranium Registries, College of Pharmacy, Washington State University,*
13 *Richland, Washington, USA.*

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15 ^c*Agilent Technologies Australia, North Ryde, New South Wales, Australia.*
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21 **Abstract**
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23 Internal exposure from naturally occurring radionuclides (including the inhaled long-lived actinides ²³²Th
24 and ²³⁸U) is a component of the ubiquitous background radiation dose¹. It is of interest to compare the
25 concentration distribution of these natural α-emitters in the lungs and respiratory lymph nodes with
26 those resulting from occupational exposure, including exposure to anthropogenic plutonium, depleted
27 and enriched uranium. This study examines the application of laser ablation-inductively coupled plasma-
28 mass spectrometry (LA-ICP-MS) to quantifying and visualizing the mass distribution of uranium and
29 thorium isotopes from both occupational and natural background exposure in human respiratory tissues,
30 and for the first time, extends this application to the direct imaging of plutonium isotopes. Sections of
31 lymphatic and lung tissues taken from deceased former nuclear workers with known history of
32 occupational exposure to specific actinide elements (uranium, plutonium or americium) were analyzed by
33 LA-ICP-MS. Using a previously developed LA-ICP-MS protocol for elemental bio-imaging of trace elements
34 in human tissue and a new software tool, we generated images of thorium (²³²Th), uranium (²³⁵U and ²³⁸U)
35 and plutonium (²³⁹Pu and ²⁴⁰Pu) mass distributions in sections of tissue. We used a laboratory-produced
36 matrix-matched standard to quantify the ²³²Th, ²³⁵U and ²³⁸U concentrations. The plutonium isotopes
37 ²³⁹Pu and ²⁴⁰Pu were detected by LA-ICP-MS in 65-μm-diameter localized regions of both a paratracheal
38 lymph node and a sample of lung tissue from a person who was occupationally exposed to refractory
39 plutonium (plutonium dioxide). The average (overall) ²³⁹Pu concentration in the lymph node was 39.2
40 ng/g, measured by High Purity Germanium (HPGe) γ-spectrometry². Localized mass concentrations of
41 thorium (²³²Th) and uranium (²³⁸U) in lymph node tissue from a person not occupationally exposed to
42 these elements (chronic natural background inhalation exposure) ranged up to 400 and 375 ng/g,
43 respectively. In lung samples of occupationally non-exposed to thorium and uranium workers, ²³²Th and
44 ²³⁸U concentrations ranged up to 200 and 170 ng/g, respectively. In a person occupationally exposed to
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3 air-oxidized uranium metal³, the maximum ²³⁵U and ²³⁸U isotopic mass concentrations in a lymph node,
4 measured at higher resolution (with a 30- μ m laser spot diameter), were 70 and 8500 ng/g, respectively.
5 The ratio of these simultaneously measured mass concentrations signifies natural uranium. The current
6 technique was not sufficiently sensitive, even with a 65- μ m laser spot diameter, to detect ²⁴¹Am (at an
7 overall tissue concentration of 0.024 ng/g, i.e., 3 Bq/g).
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14 Introduction

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17 Since its inception in 1968 as the National Plutonium Registry, the United States Transuranium and
18 Uranium Registries (USTUR) has been quantifying individual exposures to actinide elements and following
19 health outcomes in nuclear industry workers⁴. The mission of the USTUR is to study occupationally
20 exposed workers from the point of exposure to death. The USTUR measures the uptake, translocation
21 and retention (biokinetics) of plutonium, americium, uranium, and other actinides. The USTUR is also a
22 national and international resource for testing and improving the application of excreta monitoring and
23 other contemporary bioassay data to predict tissue dose rates measured at autopsy. Registered workers
24 were mostly employed at weapons sites. They received substantial accidental intakes of plutonium,
25 americium and/or uranium, since as far back as the Manhattan Project (1944-46). The USTUR and the
26 associated National Human Tissue Repository (NHRTR) is a unique resource for preserved tissues and
27 radiometric analysis data – linked to individual-specific health physics monitoring data, health records and
28 pathology findings. To date, USTUR is the custodian of tissue radioanalysis data (and preserved tissue
29 samples) from 325 donors – including 36 whole-body donors.
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38 Elemental bio-imaging (EBI) is a potential application of laser ablation-inductively coupled plasma-mass
39 spectrometry (LA-ICP-MS) for the determination of actinide distributions in human tissue samples.
40 Briefly, a focused laser beam is directed onto the surface of a tissue sample, and the ablated material is
41 transported to the ICP-MS by a carrier gas. By traversing the laser beam across the sample, the resultant
42 mass spectra can be combined into two-dimensional maps displaying the relative intensity of measured
43 isotopes throughout the tissue section. Quantitative data can be recorded by the ablation of matrix-
44 matched tissue standards and construction of multi-point calibration curves. We have previously
45 described the use of EBI in the elemental analysis of Parkinsonism animal models⁵, human osteoarthritic
46 tissue⁶ and human melanoma samples⁷.
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53 Traditionally, the measurement of plutonium (^{238,239+240}Pu) and americium (²⁴¹Am) in biological samples
54 has relied upon radiometric analysis. Radiochemical methods for the analysis of human tissues,
55 previously reported by both the USTUR and the Russian Dosimetry Registry of the Mayak Industrial
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3 Association (DRMIA), require dry/wet ashing and dissolution in mineral acids followed by radiochemical
4 separation and alpha-spectrometric detection of the actinides⁸. A similar method was used to measure
5 the plutonium content of tissues and bones from residents of Tokyo (Japan)⁹.
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9 For the past decade, ICP-MS has been established as a method for actinide bioassay, e.g., to measure the
10 concentrations of uranium isotopes in urine for both environmental¹⁰⁻¹² and occupational exposures¹³, as
11 well as environmental thorium and uranium in blood¹⁴. Recently, the application of ICP-MS for fast
12 bioassay of plutonium in feces has also been described¹⁵.
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16 LA-ICP-MS has been applied to the imaging of uranium (²³⁸U) and thorium (²³²Th) in plant materials¹⁶,
17 human brain tumour resections¹⁷, human hippocampus sections¹⁸, and in coronal rat brain sections¹⁹. It
18 was unclear if environmental exposure or another external source accounted for the presence of uranium
19 and thorium in brain tissue.
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23 This paper reports the first use of LA-ICP-MS for *in situ* imaging of the actinide elements ²³⁸U, ²³⁵U, ²³²Th,
24 ²³⁹Pu, and ²⁴⁰Pu in human lymph node and lung tissues. The LA-ICP-MS method presented in this study
25 did not require extensive or potentially biohazardous sample preparation (as is required for radiometric
26 analysis), yet it does enable concentration measurements of actinides in human tissues to be made at low
27 ng/g levels.
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34 **Experimental**

35 *Instrumentation*

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37 All experiments were carried out using a New Wave UP-213 laser ablation unit (Kenelec Technologies,
38 Mitcham, Victoria, Australia). The UP-213 emits a 213 nm laser pulse from a Nd:YAG solid state gain
39 medium. The laser unit was connected to an Agilent Technologies 7500ce ICP-MS (Forrest Hill, Victoria,
40 Australia) with a 'cs' lens system for enhanced sensitivity. The LA-ICP-MS system was tuned for maximum
41 sensitivity prior to each experiment using NIST 612 Trace Elements in Glass. NIST glass was also used to
42 ensure low oxide production. The 248/232 (ThO⁺/Th⁺) ratio was consistently less than 0.3%. Typical
43 operational parameters are given in Table 1.
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51 The laser energy density was maintained at 0.3 J cm⁻². This laser power minimized fracturing of the tissue
52 due to vaporization of water. The laser frequency was 20 Hz. Laser spot diameters were selected to
53 ensure a good balance between image resolution and sample runtime, which was up to 24 hours,
54 depending on the sample size.
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Solution nebulisation (SN)-ICP-MS was performed for the analysis and quantification of the matrix-matched tissue standards that were employed for quantification of the samples. These experiments were performed on a separate Agilent 7500 ce ICP-MS fitted with an I-AS autosampler (Agilent, Australia). A 250 ppb solution of ^{103}Rh was used as the reference element that was added to each sample via a peristaltic pump and T-piece connector. A quartz concentric nebulizer and Scott-type spray chamber (Glass Expansion, Australia) were used. Helium was used as a collision gas to remove polyatomic interferences. Parameters are outlined in Table 1.

Table 1: SN / LA-ICP-MS operational parameters.

Agilent 7500ce ICP-MS			New Wave UP213 Laser Ablation	
	LA	SN	Wavelength, nm	213
Rf Power, W	1200	1500	Repetition frequency, Hz	20
Cooling gas flow rate, L min ⁻¹	15.0	15.0	Laser energy density, J cm ⁻²	0.3
Carrier gas flow rate, L min ⁻¹	1.1	0.8	Spot size, μm	30, 65
Sample depth, mm	6.0	8.0	Scan rate, $\mu\text{m s}^{-1}$	30, 65
QP Bias, V	-5.0	-5.0	Line spacing, μm	30, 65
OctP Bias, V	-8.0	-8.0	Carrier gas	Ar
Scan mode	Peak hopping		Monitored at 30 μm , m/z	232, 235, 238
Dwell time, s per m/z	0.1	0.1	Monitored at 65 μm , m/z	232,235,238, 239, 240, 241
Extracts 1;2, V	6.8 ; -126	0; -125		
Collision gas	None	He		

Human tissue sample preparation for EBI

Samples frozen at -30°C (the standard protocol for long-term storage of NHRTR tissues) were de-frosted and fixed in 10% buffered formalin for preservation during shipment. Human tissue samples (2 samples of lung tissue and 3 lymph nodes) were received from USTUR (Table 2).

Table 2. USTUR tissue samples by case number and primary exposure element

USTUR Sample #	Tissue description	Weight (g)	Primary exposure nuclide
246.610	Lung (R) - Superior Lobe	3.22	Am
303.007	LN Tracheobronchial (R)	0.92	Pu
407.002	LN Paratracheal (R)	0.26	Pu
407.630	Lung (R) : Inferior	1.36	Pu
1060.304	LN Parabronchial (L)	0.12	U (natural)

For LA-ICP-MS measurements, the shipment formalin was decanted and samples were frozen in isopentane/liquid nitrogen and mounted in Tissue-Tek OCT freezing media (ProSciTech, Kirwan, Queensland, Australia). Samples were then sectioned at 30 μm on a cryostat using C.L. Sturkey Diamond PTFE-coated

disposable microtome blades and mounted on high-purity StarFrost microscope slides (ProSciTech). After sectioning, the remaining tissue samples were returned to the buffered formalin solution for preservation. Prepared sample sections were ablated at ambient temperature.

Thorium and uranium quantification procedure

The quantification method for thorium and uranium was adapted from Hare *et al.*⁵ as follows. Chicken breast tissue was obtained from a local market and was stripped of all fatty and connective tissue using a PTFE-coated scalpel. Approximately 5 g portions of the tissue were spiked with volumes of 100 mg/L Th and U standards in 5 % HNO₃ (Choice Analytical, Thornleigh, NSW, Australia) as listed in Table 3. A further volume of 5 % Seastar Baseline grade HNO₃ (Choice Analytical) was added to a final mass of 6 g to aid homogenization. Homogenization was performed using an OmniTech TH tissue homogenizer fitted with polycarbonate probes (Kelly Scientific, North Sydney, NSW, Australia). Six aliquots (ca. 100 mg) of accurately weighed homogenized tissue were then digested in 4:1 70 % Baseline HNO₃ (Choice Analytical) and Ultrapure 31 % H₂O₂ (Merck, Kilsyth, Victoria, Australia) using a Milestone MLS 1200 closed vessel microwave digester. The digests were gravimetrically diluted to ca. 50 g with 18.2 mΩ deionised H₂O. These digests were quantified by solution nebulisation ICP-MS. Standards for quantification were prepared from fresh 1000 ppm stocks (Choice Analytical) to determine the total uranium and thorium content of the digests (including any U and Th endogenous to the sample prior to spiking). The %RSD for the 6 aliquots was calculated (< 5%) to ensure homogeneity. These standards were then packed into 1 cm² histology moulds, frozen in liquid nitrogen/isopentane and sectioned on a cryostat. Calibration curves for LA-ICP-MS were constructed by ablating representative areas of each of the standards prior to the analysis of each sample.

Table 3: Spiked volumes and final concentrations of matrix-matched tissue standards.

	Approximate spiked volume of 100 mg/L standard solution (μL)	Final concentration (ng/g)
Th	10	171.8
	100	1537
U	10	130.9
	100	1812

Qualitative analysis of plutonium isotopes

^{239,240}Pu isotopic standard solutions are not currently available in Australia. Therefore, the results are presented as the raw signal intensity values (cps) for m/z = 239, 240.

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4 *Image construction*
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7 A laser spot size of 65 μm and scan speed of 65 $\mu\text{m s}^{-1}$ was used in all cases, except USTUR Case 1060
8 (occupational exposure to uranium) for which a laser spot size of 30 μm and scan speed of 30 $\mu\text{m s}^{-1}$ were
9 also used to produce higher resolution images. The MS integration time was set in each experiment to
10 ensure true image resolution was as close to 65 μm (or 30 μm) as possible. Images were subsequently
11 produced using in-house ISIDAS (Interactive Spectral Imaging Data Analysis Software) suite written in
12 Python programming language to reduce all MS scan data into two-dimensional images. These images
13 were exported from ISIDAS as Visualization Toolkit (.vtk) files into the MayaVi2 (Enthought, Inc., Austin,
14 Texas, USA) for final image rendition.
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23 *Sample case descriptions*
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25 USTUR Case 0407
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27 This gentleman was employed at the Rocky Flats Plutonium Fabrication Plant in Colorado, USA from 1958
28 to 1975²⁰. In 1965 he was involved in an extensive plutonium fire incident. Examination of the plutonium
29 fire aerosol showed that the material was highly refractory (insoluble) and this was avidly retained in the
30 lungs. For this reason intravenous chelation therapy with calcium diethylenetriaminepentaacetic acetate
31 (Ca-DPTA) was ineffective, and the Registrant was reassigned to non-plutonium work. There is no record
32 of this registrant having worked with uranium or thorium. He passed away in 2008 at age 90+ years from
33 heart failure. This Registrant was a whole body donor and the lung and lymph node samples studied here
34 were taken at autopsy.
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41 USTUR Case 0303
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43 Case 0303²¹ was employed for 30 years at the Hanford complex. He was involved in several minor
44 plutonium exposures and a major exposure in 1968, when he punctured his protective glove and cut his
45 finger on Pu-contaminated equipment. The wound was heavily contaminated with soluble plutonium.
46 Tissue surrounding the wound was excised and intravenous administration of Ca-DPTA enhanced his
47 urinary excretion of plutonium. He did not work with uranium. The Registrant died in 2008 at age 87. A
48 tracheobronchial lymph node (taken at autopsy) was studied here.
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53 USTUR Case 0246
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55 This Registrant was employed at the Hanford nuclear materials complex in Washington, USA for 25
56 years²². In 1976 an ion-exchange column containing approximately 100 g of ²⁴¹Am that he was working on
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3 exploded, causing him severe acid burns and cuts to his face and upper body. Intravenous Ca-DPTA
4 treatment was commenced promptly, followed by several years of intravenous Zn-DPTA chelation
5 therapy. The Registrant died in 1987 at 75 years of age, from emphysema. Prior to his accidental ²⁴¹Am
6 exposure, he had suffered a myocardial infarction and coronary artery disease. A right lung superior lobe
7 (taken at autopsy) was studied here.
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12 USTUR Case 1060
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14 This Registrant worked at the Hanford complex for 40 years, where he was chronically exposed to
15 uranium from 1948 to 1950 whilst working in the uranium melt plant²³. The form of the uranium was
16 most likely U₃O₈. Urinalysis suggested there was a single acute incident of uranium exposure occurring in
17 1948 in addition to chronic U dietary intake. This Registrant was also involved in several plutonium
18 contamination incidents and was potentially exposed to elevated airborne plutonium concentrations on
19 two occasions, but only one urine measurement exceeded the minimum detectable activity (MDA) for
20 plutonium. The Registrant died (in 2008) at age 83, of a cerebral infarct due to thrombosis of the left
21 carotid artery. A left parabranchial lymph node (taken at autopsy) was studied here.
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30 Results and discussion 31

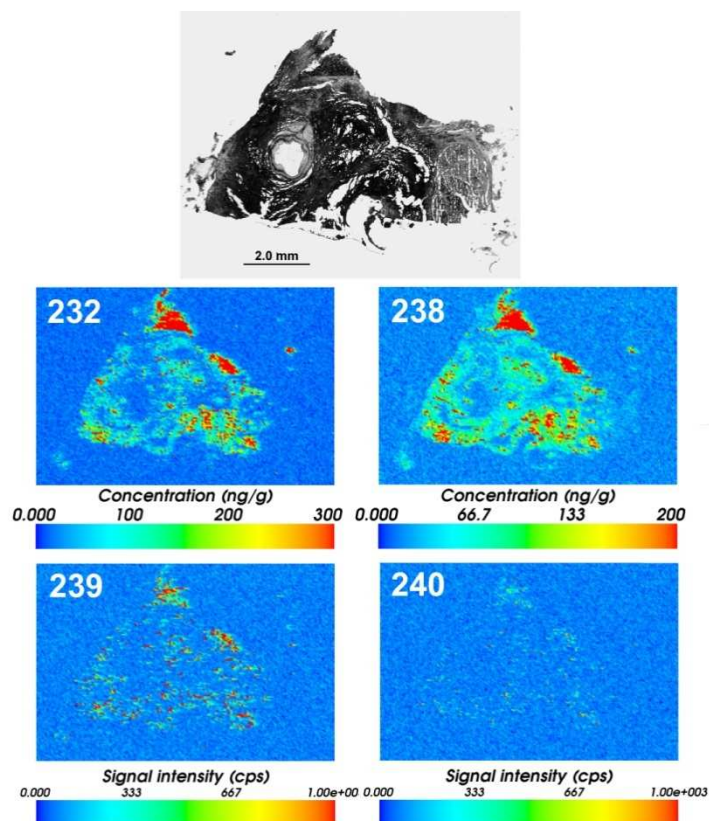
32 *Plutonium exposure* 33

34 *USTUR Case 0407* 35 36

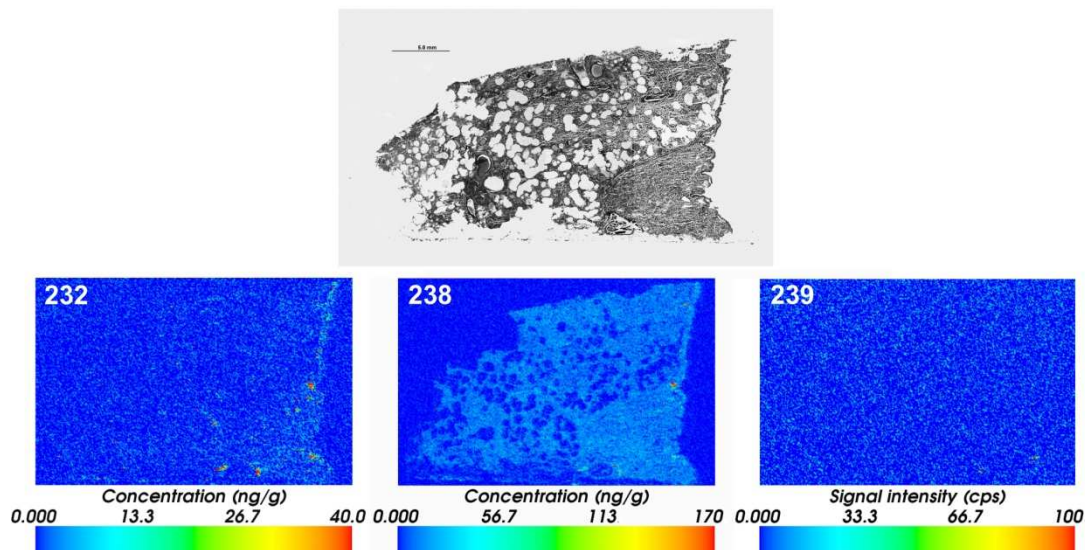
37 Figure 1 shows a light micrograph and images of m/z 232, 238, 239 and 240 in the paratracheal lymph
38 node from Case 0407. Lateral image resolution was 65 μm. The m/z 239 and 240 images represent ²³⁹Pu
39 and ²⁴⁰Pu, respectively. The relative intensities of the 239 and 240 signals are consistent with ²⁴⁰Pu/²³⁹Pu
40 atom ratio (0.02 – 0.08) expected for weapons grade plutonium²⁴. From γ-spectrometric measurements,
41 the average ²³⁹Pu concentration in the whole lymph node was estimated to be 39 ng/g. ²⁴¹Am was not
42 detected by LA-ICP-MS as the average ²⁴¹Am concentration (0.2ng/g) estimated by γ-spectrometry was
43 below the estimated 1 ng/g detection limit of the instrument. The signal at m/z = 239 was solely due to
44 ²³⁹Pu and not the ²³⁸UH⁺ isobaric ion, as a signal at 239 was not detected in other samples with high
45 concentrations of ²³⁸U such as Case 1060 (8500 ng/g).
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52 Figure 1 clearly indicates inhomogeneous distribution of all measured actinides in the lymph node, with
53 very similar localization of ²³²Th and ²³⁸U (presumably from chronic natural background inhalation
54 exposure) to that of anthropogenic ²³⁹Pu and ²⁴⁰Pu (from occupational exposure). The measured ²³²Th
55 concentration ranged up to 300 ng/g.
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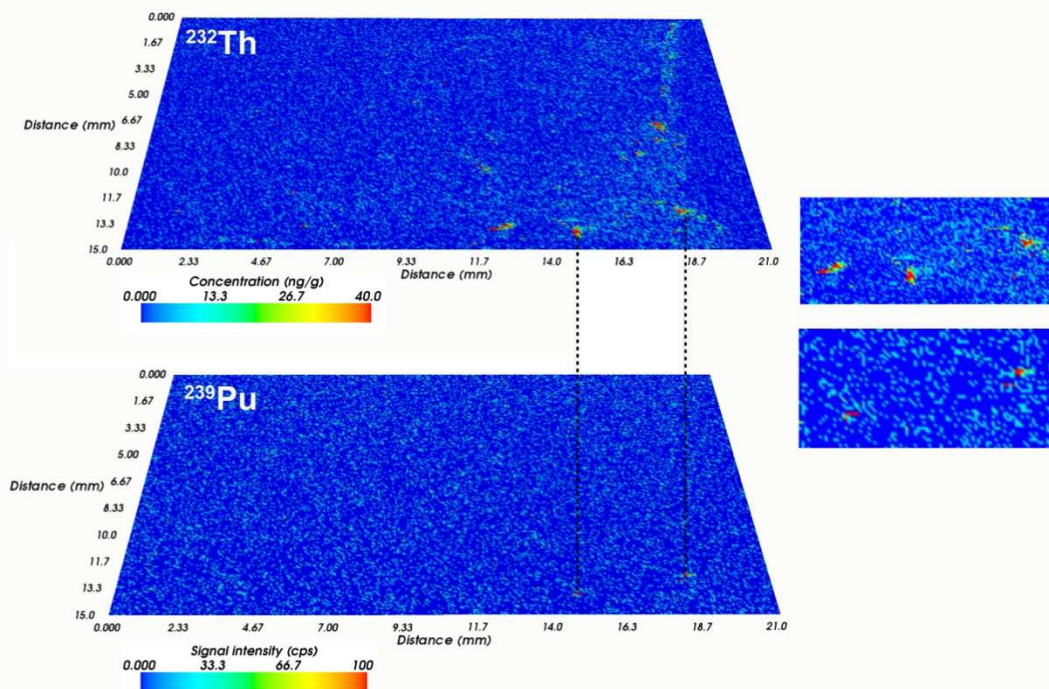
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3 An inhomogeneous actinide distribution was also found in the lung (Figure 2). This lung segment from the
4 inferior right lobe shows two distinctive areas of signal at $m/z = 239$, with no corresponding signal
5 recorded for $m/z = 240$. Figure 3 shows that the location of the $m/z=239$ signal (^{239}Pu) from acute
6 accidental inhalation was correlated with that of $m/z = 232$ (^{232}Th) from chronic background inhalation.
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42 **Figure 1:** Photomicrograph (top) and m/z 232, 238, 239 and 240 images (65- μm scan spot) of paratracheal
43 lymph node from USTUR Case 0407.
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24 **Figure 2:** Photomicrograph (top) and 232, 238 and 239 images (65- μ m scan spot) from inferior right lung
25 segment (approx. 3 cm long) from USTUR Case 0407.



52 **Figure 3:** Corresponding m/z 232 and 239 particles in inferior right lung tissue in USTUR Case 0407.

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USTUR Case 0303

This Registrant had suffered a skin puncture wound contaminated with a soluble form of plutonium. This incident may also have released some airborne plutonium. The right tracheobronchial lymph node showed no detectable quantities of Pu-material at m/z 239 or 240. This confirmed the soluble nature of any inhaled plutonium.

Figure 4 shows a distribution of ^{232}Th and ^{238}U in the lymph node ranging up to 400 and 375 ng/g, respectively. Lateral image resolution was 65 μm . The Registrant did not work with these nuclides, and so the measured levels reflect his chronic (presumably natural) background inhalation exposure. These ^{232}Th and ^{238}U maximum concentrations are close to the values measured in the lymph node from Case 0407 of (300 ng/g and 200 ng/g, respectively), who also did not work with these radionuclides. It was extremely unlikely that the measured ^{232}Th concentrations in the lymph node arose from adventitious exposure at the Rocky Flats and Hanford sites since this material was not involved in their production processes. The measured ^{238}U concentrations are similar to those of ^{232}Th , and are thus also most likely to have arisen from chronic (natural) background inhalation of uranium.

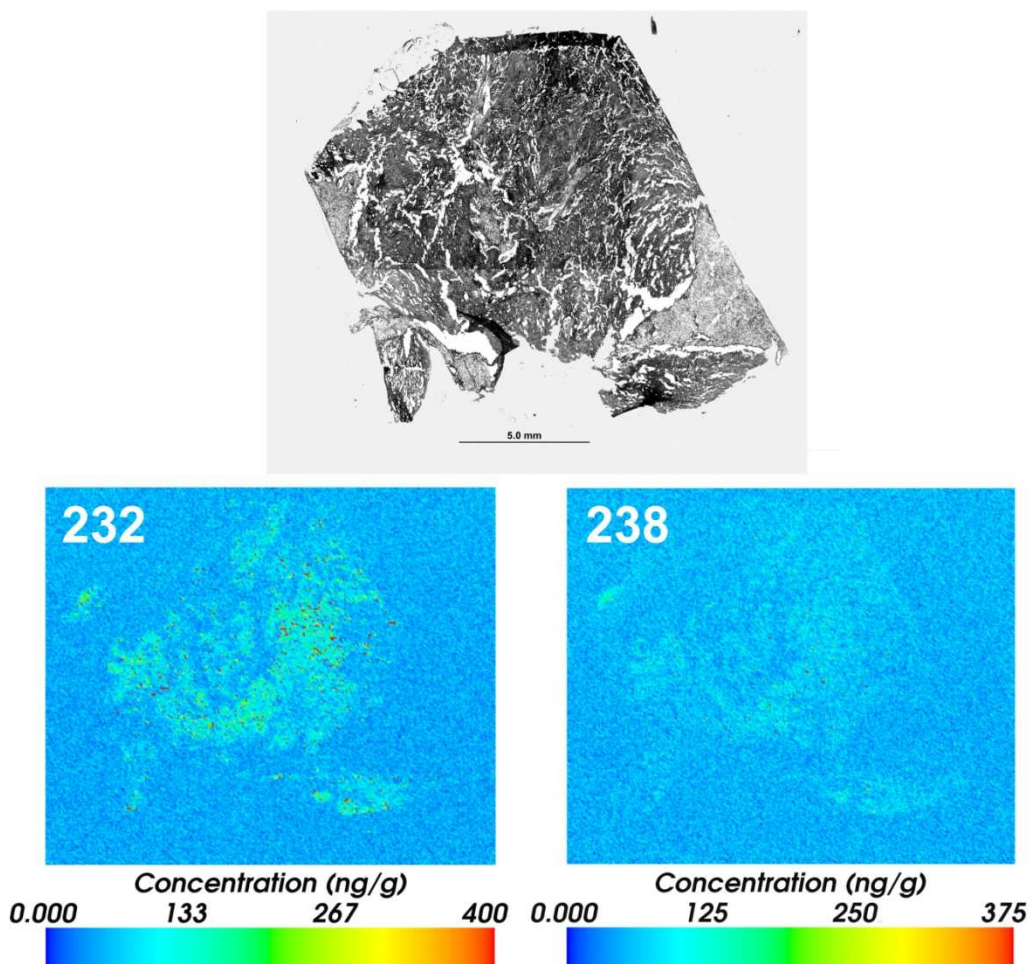


Figure 4: Photomicrograph (top) and m/z 232 and 238 images (65- μ m scan spot) of right tracheobronchial lymph node from USTUR Case 0303.

Americium exposure

USTUR Case 0246

^{241}Am was not detected in the section of right superior lung lobe analyzed here. This null observation is consistent with previous radiochemical ^{241}Am analyses (3 Bq/g or 0.024 ng/g) in the right lung²⁵. This concentration is well below the limit of detection of the currently used LA-ICP-MS system. However, as for the two earlier cases, inhomogeneous distributions of ^{232}Th and ^{238}U , presumably from chronic natural background inhalation were observed, with concentrations ranging up to 200 ng/g and 100 ng/g, respectively (Figure 5).

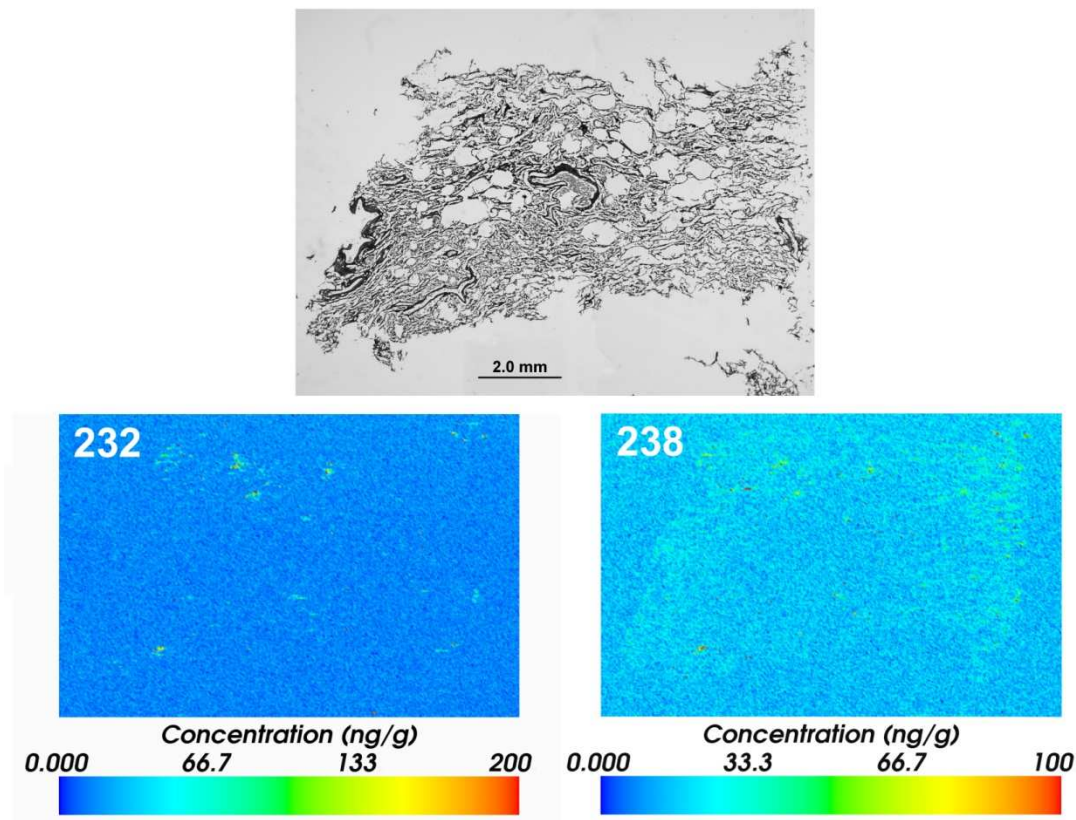


Figure 5: Photomicrograph (top) and ^{232}Th and ^{238}U images (65- μm scan spot) from superior right lung tissue from USTUR Case 0246.

Uranium and thorium exposure

USTUR Case 1060

The parabranchial lymph node from Case 1060 (Figure 6) showed ~20 – 40 times higher ^{238}U concentration than the lymph nodes from Cases 0303 and 0407. Furthermore, ^{235}U was detected in the Case 1060 lymph node. The high measured values of ^{238}U and detectability of ^{235}U , and low ^{232}Th are consistent with this Registrant's known occupational exposure to uranium but not to thorium.

Table 4 compares the maximum ^{232}Th , ^{235}U and ^{238}U concentrations measured for Case 1060 with those measured for the other three USTUR cases.

Table 4. Comparison of ^{232}Th , ^{235}U and ^{238}U tissue concentrations from natural background and occupational uranium exposures in former nuclear workers

USTUR Sample #	Tissue description	Type of exposure	Maximum isotopic concentration, ng/g		
			^{232}Th	^{235}U	^{238}U
1060.304	LN Parabronchial (L)	occupational [†]	160	70	8500
0246.610	Lung (R) - Superior Lobe	chronic natural	200	N.D. [‡]	100
0303.007	LN Tracheobronchial (R)	chronic natural	400	N.D.	375
0407.002	LN Paratracheal (R)	chronic natural	300	N.D.	200
0407.630	Lung (R) : Inferior	chronic natural	40	N.D.	170

[†]- chronic exposure to natural ^{232}Th , [‡] - not detected

As shown in Table 4, the maximum concentration of ^{232}Th in lung from (presumed) natural background inhalation exposure ranged within 40 – 200 ng/g and within 160 – 400 ng/g in lymph node samples. No ^{235}U was detected in either lymph node or lung samples from cases with these low background exposures and the ^{238}U concentration in lungs (100 – 170 ng/g) was about half that in lymph nodes (200 – 375 ng/g).

USTUR Registrant 1060 was chronically exposed to uranium of natural composition at work³ for several years, with a single acute high-level exposure²³.

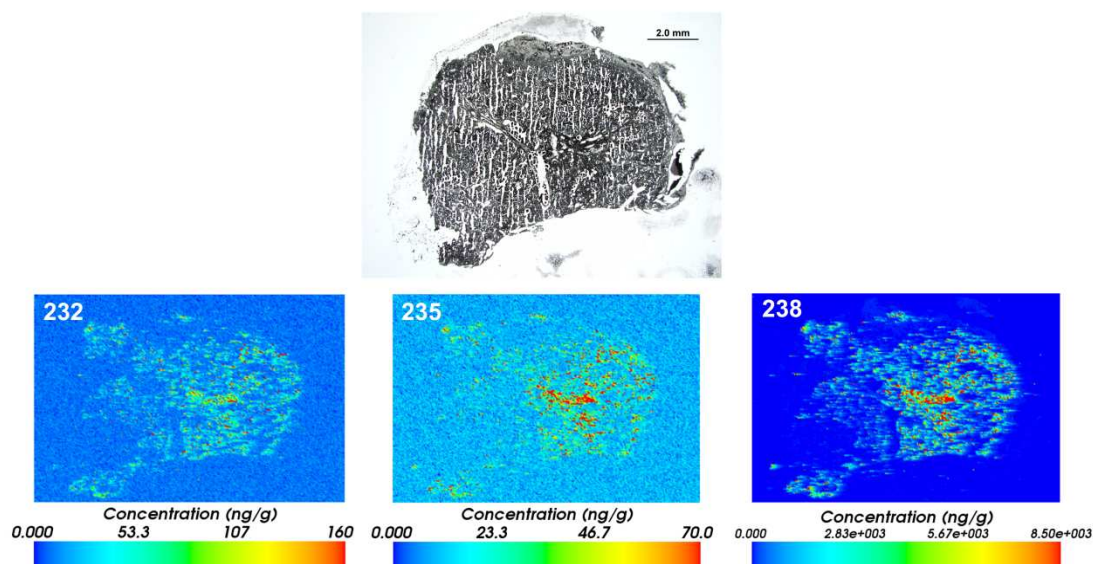


Figure 6: Photomicrograph (top) and m/z 232, 235 and 238 images (30- μm scan spot) of left parabronchial lymph node from USTUR Case 1060.

Case 1060 was also reported to have had exposure to airborne Pu on two occasions, although no ^{239}Pu or ^{240}Pu was detected in the lymph node. This null observation is consistent with the health physics monitoring data in this case, which recorded only one positive measurement of Pu in urine²³. However, non-detection of any signal at $m/z = 239$ in this high uranium exposure case (at 8500 ng/g ^{238}U) is important, since it confirms that the $m/z = 239$ signal in Case 0407 is entirely attributable to the ^{239}Pu and not to $^{238}\text{UH}^+$ isobaric interference.

Conclusion

Elemental bio-imaging by LA-ICP-MS is a useful tool for both visualization and quantitative determination of the localized mass concentrations of the actinide elements Th and U in human tissues, for both chronic natural background and occupational exposures. For the first time, qualitative bio-imaging of ^{239}Pu and ^{240}Pu is demonstrated for lymph node and lung samples from an occupationally exposed person. The distributions of thorium, uranium and plutonium isotopes in all sections of lymph node and lung analyzed were highly inhomogeneous, indicating localized aggregation of the inhaled particles for both chronic natural background and acute occupational actinide exposures. This work provides a significant new capability to study the micro-distribution of long-lived actinides in human tissues, and thus directly address issues of non-uniformity of radiation dose. Furthermore, we are extending the method to the field of industrial hygiene for former nuclear workers, in particular to the localization and quantification of beryllium, and potentially asbestos, in lung and lymph nodes.

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