A STUDY OF $^{219}\text{Rn}$ OUTGASSING AND $^{211}\text{Pb}$ CONTAMINATION FROM $^{223}\text{Ra}$ IN DRY, LIQUID, AND MURINE TISSUE SAMPLES

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Abstract—Introduction: A study of $^{211}\text{Pb}$ contamination caused by the outgassing of $^{219}\text{Rn}$ from $^{223}\text{Ra}$ in dry, liquid, and murine tissue samples has been made to help design proper handling procedures for $^{223}\text{Ra}$ in preclinical biodistribution work. Materials and Methods: $^{211}\text{Pb}$ activity levels were measured from $^{223}\text{Ra}$ in dry, liquid, and tissue samples using aspiration and autoradiography techniques. Results: Using aspiration techniques on dry samples of $^{223}\text{Ra}$, an average $^{219}\text{Rn}$ outgassing rate of $51\% \pm 21\%$ was measured with one measurement reaching as high as $81\%$. $31\% \pm 4\%$ $^{211}\text{Pb}$ contamination was measured within a 4.3 cm radius of a dry $^{223}\text{Ra}$ source placed inside a 10-cm-diameter petri dish where the lip of the petri dish contained the $^{219}\text{Rn}$ dissemination. Without the containment of the petri dish, $^{219}\text{Rn}$ can reach as far as 7.8 cm from the source with trace levels spreading further. Using aspiration techniques on liquid samples of $^{223}\text{Ra}$, outgassing rates of $^{219}\text{Rn}$ were $0.9\% \pm 0.3\%$. The outgassing levels in harvested organs from a biodistribution were as high as $10.1\% \pm 0.4\%$ for an intraperitoneally injected mouse and $0.204\% \pm 0.006\%$ for an intravenously injected mouse. The outgassing of the intravenously injected mouse carcass was less than $0.1\%$. Conclusion: In dry form, the high levels of $^{219}\text{Rn}$ outgassing from a $^{223}\text{Ra}$ source necessitate the use of ventilated biohoods when handling or preparing $^{223}\text{Ra}$ from source vials. The very low levels of $^{219}\text{Rn}$ outgassing from $^{223}\text{Ra}$ liquid sources reduces exposure to $^{219}\text{Rn}$ by a factor of 50. $^{219}\text{Rn}$ exposure from murine organ tissue reaches levels of $10\%$ when handling organs from an intraperitoneal injection and less than $0.2\%$ for an intravenous injection.

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INTRODUCTION

$^{223}\text{Ra}$ has become an important new therapy for osteoblastic bone metastases caused by cancer (Goyal and Antonarakis 2012). However, because it is an alpha-emitting radiotracer, it can be difficult to study with conventional radionuclide methods. Nevertheless, to understand how to optimize its use, preclinical studies are important. As is known from the decay of $^{223}\text{Ra}$, $^{219}\text{Rn}$ is the first decay product in the decay chain that is of concern since it is an inert gas which can contaminate the lab bench or immediate areas, including the person handling the activity. The worst case would be direct inhalation of $^{219}\text{Rn}$ or its decay progeny by the person handling samples of $^{223}\text{Ra}$. In the initial studies of $^{219}\text{Rn}$ contamination and dissemination, it was observed that just placing a 37 kBq $^{223}\text{Ra}$ dry source on the benchtop for 30 min and then removing it would leave a contamination imprint that would trigger a handheld ZnS meter. This raised the question as to what the contamination was, how widespread could it be, and the nature of the dissemination from the source.

A review of the literature on $^{219}\text{Rn}$ outgassing from $^{223}\text{Ra}$ in a preclinical laboratory setting resulted in very few publications on this topic. There are many publications on the source and dissemination of $^{222}\text{Rn}$ and $^{220}\text{Rn}$ from the ground, in mines, and in other nonlaboratory settings (Ball et al. 1991). Therefore, to answer these initial questions, a comprehensive study was undertaken of $^{219}\text{Rn}$ contamination in the framework of performing preclinical studies with $^{223}\text{Ra}$. Typical injected doses are on the order of 37 kBq, which drove the scale of the study by limiting the exposure levels to around the 37 kBq level. The goal of the study was to understand how much $^{219}\text{Rn}$ outgasses from $^{223}\text{Ra}$ as a dry source or in solution. A further goal of the study was to quantify the outgassing from tissue samples since the main work of preclinical studies involves as little as 10...
and up to 50 or more mice in a single biodistribution study, which could lead to significant exposure to alpha radiation from $^{219}$Rn outgassing when the mice are sacrificed and dissected and their organs are harvested, exposing a lot of tissue that could potentially outgas $^{219}$Rn.

The study involved developing methods to measure the outgassing of $^{219}$Rn from a $^{223}$Ra source, learning how to properly quantify activity levels of $^{211}$Pb, and developing methods to measure the dissemination of $^{219}$Rn from a $^{223}$Ra source. These methods were used to measure the levels of $^{219}$Rn outgassing from mouse tissue samples.

A $^{223}$Ra atom will undergo six decays before it reaches the stable radionuclide $^{207}$Pb. Fig. 1 shows the decay sequence of $^{223}$Ra (Aitken-Smith and Collins 2016). From a practical perspective, when handling $^{223}$Ra, the radionuclide will emit the inert gas $^{210}$Rn. This $^{210}$Rn then will disseminate or outgas from the $^{223}$Ra source as a plume a few centimeters in size assuming no airflow around the source, with the plume size determined by the short 3.96 s half-life of $^{219}$Rn. Within the $^{219}$Rn gas plume, $^{215}$Po atoms will appear from the decay of $^{219}$Rn. The $^{215}$Po atoms only have a 1.78 ms half-life and therefore disappear almost immediately and decay into relatively longer-lived $^{211}$Pb, which has a half-life of 36.1 min. Because of this relatively long 36.1 min half-life and being metallic, $^{211}$Pb will precipitate out of the air and settle onto whatever material is found around the $^{223}$Ra source. The $^{211}$Pb will then undergo the decay sequence $^{211}$Pb $\rightarrow$ $^{211}$Bi (36.1 min half-life), $^{211}$Bi $\rightarrow$ $^{207}$Tl (2.17 min half-life), and $^{207}$Tl $\rightarrow$ $^{207}$Pb (4.77 min half-life). Two alternate decay chains have been ignored since the branching ratio is so small: $^{215}$Po $\rightarrow$ $^{215}$At, which has a 0.00023% branching ratio; and $^{211}$Bi $\rightarrow$ $^{211}$Po, which has a 0.276% branching ratio. Four alpha and two beta particles are emitted from the decay chain, resulting in the total energy emission of 27.3 MeV. Refer to Table 1 for details of the $^{223}$Ra decay chain (Stabin and da Luz 2002).

Before diving into the study of $^{219}$Rn outgassing and dissemination, a quick overview of the exposure limits for $^{223}$Ra and the relevant decay progeny is important to understand the different levels of activity that could cause harm from exposure. Of the three radionuclides of concern in this study, $^{223}$Ra, $^{219}$Rn, and $^{211}$Pb, the US Nuclear Regulatory Commission (NRC) has published an annual limit on intake (ALI) for inhaling $^{223}$Ra, which is 26 kBq, and for

![Fig. 1. $^{223}$Ra decay chain. A total of four alphas and two betas are emitted before a $^{223}$Ra atom decays to the stable $^{207}$Pb. Two alternate decay paths of $^{215}$Po $\rightarrow$ $^{215}$At and $^{211}$Bi $\rightarrow$ $^{211}$Po are ignored since their branching fractions are so small.](www.health-physics.com)
Table 1. Table of the energy emissions per decay. The data are extracted from the RADAR decay data (Stabin and da Luz 2002) spreadsheet found at https://www.doseinfo-radar.com/RADARDecay.html. These are the branching fraction weighted energy emissions broken down by emission type.

| Radionuclide | 223Ra | 219Rn | 215Po | 211Pb | 211Bi | 209Tl |
|--------------|-------|-------|-------|-------|-------|-------|
| Half-life    | 11.43 d | 3.96 s | 1.78 ms | 36.1 min | 2.17 min | 4.77 min |
| Abundance in a 223Ra sample (%) | 9.97 $\times 10^{-6}$ | 4.01 $\times 10^{-6}$% | 1.80 $\times 10^{-1}$% | 2.19 $\times 10^{-1}$% | 1.32 $\times 10^{-2}$% | 2.90 $\times 10^{-2}$% |
| Alpha (MeV disintegration$^{-1}$) | 5.77 | 6.75 | 7.39 | 6.55 |
| Beta (MeV disintegration$^{-1}$) | 0.450 | 0.00049 | 0.495 |
| Electron capture (MeV disintegration$^{-1}$) | 0.0664 | 0.00648 | 0.00414 | 0.0126 |
| Gamma (MeV disintegration$^{-1}$) | 0.134 | 0.0575 | 0.00018 | 0.0635 | 0.0474 | 0.00233 |
| Total | 5.98 | 6.82 | 7.39 | 0.518 | 6.61 | 0.498 |
| Parent + progeny—alpha (MeV disintegration$^{-1}$) | 26.5 | 20.7 | 13.9 | 6.55 | 6.55 | 0 |
| Parent + progeny—beta (MeV disintegration$^{-1}$) | 0.946 | 0.946 | 0.946 | 0.946 | 0.496 | 0.495 |
| Parent + progeny—electron capture (MeV disintegration$^{-1}$) | 0.0896 | 0.0232 | 0.0168 | 0.0168 | 0.0126 | 0 |
| Parent + progeny—gamma (MeV disintegration$^{-1}$) | 0.305 | 0.171 | 0.113 | 0.113 | 0.0497 | 0.00233 |
| Parent + progeny—total (MeV disintegration$^{-1}$) | 27.8 | 21.8 | 15.0 | 7.63 | 7.11 | 0.498 |
| Biological equivalent weighted parent + progeny (MeV disintegration$^{-1}$) | 134 | 105 | 70.8 | 33.8 | 33.3 | 0.498 |
| Biological equivalent weighting factor | 4.81 | 4.80 | 4.71 | 4.44 | 4.67 | 1.000 |

211Pb, which is 22.2 MBq (US NRC 2014). This dose will reach a 0.05 Sv whole-body exposure for a radiation worker, which is the limit defined by the US NRC. There is no published ALI for 219Rn. At first blush, one should be very careful when working with 223Ra since only one inhaled dose of 26 kBq exposes the radiation worker to the US NRC annual limit. When working with preclinical studies, 26 kBq is on the order of one injection dose, which is just one in many when doing a comprehensive preclinical study that typically involves many tens of mice. However, the chance of inhaling that much activity of 223Ra is very improbable. The risk is inhalation of 219Rn.

When calculating the worst-case scenario in which all the 219Rn gas from a 37 kBq 223Ra source is inhaled over the course of say, 1 h, the whole-body effective dose exposure is just 0.27 mSv due to the short 3.96 s half-life of 219Rn, and that amounts to only a small fraction of the US NRC limit of 50 mSv. This whole-body effective dose from the direct inhalation of 219Rn was calculated using the following formula for absorbed dose:

$$D_{Gy} = 1.602 \times 10^{-10} \frac{A_{Bq} t_s \varepsilon_{MeV}}{M_g},$$  \hspace{1cm} (1)

where $D_{Gy}$ is the absorbed dose in Gy, $A_{Bq}$ is the activity of the radionuclide in Bq, $t_s$ is the exposure time in s, $\varepsilon_{MeV}$ is the energy released per decay, and $M_g$ is the mass of the tissue or organ in g. The biological equivalent dose is calculated by applying the suitable radiation emission weights for alphas, betas, and gammas emitted through the full chain of decays. The weighting factor of 5 is used for alpha emissions which is taken from the OLINDA dosimetry software package (Stabin et al. 2005).

Using a simplistic model in which only the lungs received the dose, the effective dose $D_{SV}$ is:

$$\text{Effective dose } D_{SV} = 0.12 \times D_{SV} = 0.12 \times 4.79 \times D_{Gy}. \hspace{1cm} (2)$$

Plugging in the numbers for 37 kBq, an exposure time of 3,600 s, the total emission energy of 21.8 MeV for the full decay chain of 219Rn, and 1,000 g for the mass of the lungs into eqns (1) and (2), one arrives at 0.27 mSv. Therefore, direct inhalation exposure to 219Rn at the 37 kBq level for 1 h is rather benign. Nevertheless, since the outgassing levels of 219Rn from a dry 37 kBq 223Ra source were so high, with the resulting 211Pb contamination tripping a handheld ZnS alpha meter, we embarked on this study to get a better picture of the extent of contamination under various conditions relevant to biodistribution studies to improve the handling methods of 223Ra and the tissue samples from the bio distribution studies.

The goal of this study is to quantify how much contamination is generated from 223Ra and what is the extent of
contamination when it is used in conjunction with a typical preclinical biodistribution animal study in which the radionuclide is administered either by an intraperitoneal (IP) injection or an intravenous (IV) injection. The handling steps include preparing the $^{223}$Ra solution, most likely starting with a source vial containing $^{223}$Ra dichloride; injecting the radionuclide into the mouse; sacrificing the mouse; harvesting the tissues; and potentially exposing workers to radiation from the tissue and blood from the mouse dissections.

Contamination from the outgassed $^{219}$Rn and resulting $^{211}$Pb were measured as a percent of the activity of the $^{223}$Ra source. It was assumed that 100% of the airborne $^{219}$Rn will convert to $^{211}$Pb after secular equilibrium has been reached; therefore, by measuring the activity rate of $^{211}$Pb, one will be measuring the activity rate of $^{219}$Rn. Two methods, which are detailed in the Materials and Methods section, were developed to measure $^{211}$Pb activity. The first used aspiration as a method to capture the outgassed $^{219}$Rn from a $^{223}$Ra source. The $^{219}$Rn, which converts to $^{211}$Pb, was adsorbed by a carbon filter that was placed in the aspiration hose. Other techniques to collect $^{211}$Pb have been reported in the literature (Atcher et al. 1989). To measure ambient $^{211}$Pb diffusion from a $^{223}$Ra source, autoradiograph techniques were used. Sheets of paper were exposed to $^{211}$Pb by placing a $^{223}$Ra source on the sheet for 2 to 3 h. The $^{223}$Ra source was then removed from the sheet, and the sheet was exposed to photostimulable phosphor (PSP) autoradiograph plates from which one can get a quantitative image of the spatial $^{211}$Pb distribution on the sheet. Again, it was assumed that once secular equilibrium was reached, the $^{211}$Pb activity level was a proxy for measuring the amount of $^{219}$Rn outgassing from the $^{223}$Ra source. The results will be presented as percent activity levels of $^{211}$Pb relative to the $^{223}$Ra source activity. Note that since $^{211}$Pb activity measurements were used as a proxy for $^{219}$Rn activity levels, references to $^{211}$Pb or $^{219}$Rn activity levels are used interchangeably. Keep in mind that there were no direct measurements of $^{219}$Rn activity made in this study, as all measurements were of $^{211}$Pb activity levels.

The handling of the mice in preparation of the tissue samples were performed in accordance with National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals using institutional animal care and use committee (IACUC)-approved protocols (NRC/NAS 2011).

**MATERIALS AND METHODS**

Key to studying the exposure of radioactive contaminants resulting from $^{223}$Ra and its decay progeny is to be able to accurately measure activity levels of $^{223}$Ra and $^{211}$Pb samples. This was done using an Ortec GEM10P4-70 high-purity germanium (HPGe) detector (Oak Ridge, Tennessee, US), a microdose calibrator (Adler and Choyke 2018) developed in house, and a Fuji Film FLA-5100 fluorescent/radioisotopic autoradiograph imaging system (Fujifilm Life Science, Singapore). This study used the HPGe detector to prepare $^{223}$Ra and $^{211}$Pb standards used to calibrate the microdose calibrator, which in turn was used to calibrate the images generated by the FLA-5100 autoradiograph imaging system.

Performance tests of the HPGe detector were made to measure its activity and volumetric linearity. It was determined that the HPGe detector activity measurements were accurate to within ±2.5% for sample volumes under 16 μL, and dead-time corrections were accurately applied within ±2.5% up to raw input counting rates of 18 kcps. Nevertheless, with the measured dead time of 50% at a raw input count rate of 18 kcps, it was determined to limit the dead time to 20% by keeping all measurements under a raw input count rate of 5 kcps. An updated set of $^{223}$Ra gamma emission branching fractions, used in calculating $^{223}$Ra activity rates, were adopted from Pibida et al. (2015). The HPGe is calibrated to measure activity in solutions approximating a point source geometry. To measure the activity in air filter pellets, a volume correction was measured to be 0.813 ± 0.015 (1.86%) to correct for the air filter pellet geometry. Samples of $^{223}$Ra and $^{211}$Pb were prepared and measured on both the HPGe detector and the microdose calibrator. This provided $^{223}$Ra and $^{211}$Pb calibration factors for the microdose calibrator of 1.06 ± 0.02 (2%) and 6.48 ± 0.13 (2%), respectively. For the autoradiograph imaging system, several $^{211}$Pb-contaminated sheets were exposed to phosphor plates for half an hour and developed. The sheets were measured in the microdose calibrator, and the integrated total photostimulated luminescence (PSL) units were measured in the autoradiograph images for each sheet. A calibration factor of (4.07 ± 0.12) × 10⁻³ Bq PSL⁻¹ was measured.

To obtain samples of $^{211}$Pb, an aspiration system was developed to capture the $^{211}$Pb on the carbon pellets of an air filter resulting from the $^{219}$Rn gas decay product in the first decay step of $^{223}$Ra. The $^{223}$Ra source was made by placing a few microliters of $^{223}$Ra solution on a 24-mm-diameter circular glass fiber filter (catalog number 1822-024; Whatman/GE Healthcare, Brentford, Middlesex, UK) that was subsequently set aside to dry. A cone aspirator designed to hold the glass fiber filter was three-dimensionally (3D) printed. The aspirator was connected to a vacuum hose, which has one or more carbon air filters placed in series along the length of the hose. The vacuum was set to aspirate at a rate of 4 L min⁻¹. The dry $^{223}$Ra source was placed in the cone aspirator with the vacuum pump enabled and left for 2 to 3 h to allow the accumulation of $^{211}$Pb in the air filters to reach secular equilibrium. Fig. 2 shows photographs of the dry $^{223}$Ra glass fiber filter.
source, the 3D-printed cone aspirator, and the air filters placed in series along the aspiration hose. Once the level of $^{211}\text{Pb}$ approaches its maximum activity in the carbon filter, the carbon pellets are removed from the air filter and placed in a 20 mL glass scintillation vial where the activity can be measured in the microdose calibrator.

Using the $^{223}\text{Ra}$ aspiration system, two studies to measure the efficiency of $^{211}\text{Pb}$ collection in the air filters were done. The first was to measure the rate at which the accumulation of $^{211}\text{Pb}$ in the aspiration system approaches maximum activity. This was done by measuring the $^{211}\text{Pb}$ accumulation in the first air filter as a function of aspiration time. The aspirations were repeated with aspiration times varying between 5 and 160 min, doubling the time for each repeated aspiration. The goal of the second study was to quantify the total $^{211}\text{Pb}$ emitted from the $^{223}\text{Ra}$ source. This was done by placing at least four carbon filters in series in the vacuum hose and aspirating the source for at least 2 h. At the end of the aspiration period, the carbon pellets and foam padding from each of the air filters were placed in preweighed 20 mL glass vials. The carbon pellets and foam padding were placed in separate 20 mL vials. The $^{223}\text{Ra}$ glass fiber filter source was removed from the aspiration cone and placed in its own 20 mL glass vial. The $^{211}\text{Pb}$ activity in the cone, the 20 mL vials containing the carbon pellets and foam paddings, as well as the $^{223}\text{Ra}$ activity of the paper filter were measured in the microdose calibrator.

For both studies, the equation of the form

$$f(x) = A \left(1 - e^{-x \ln(2)/x_{1/2}}\right),$$

was used to describe the collection of $^{211}\text{Pb}$ over time or the total adsorption of $^{211}\text{Pb}$ on carbon pellets. In the former
case, \( x \) stands for aspiration time, \( x_{1/2} \) is the time the \(^{211}\text{Pb} \) reaches half-way to its maximum activity plateau, and \( A \) is the \(^{211}\text{Pb} \) activity at the plateau. In the latter case, \( x \) stands for the weight of the carbon pellets in g, \( x_{1/2} \) is the weight of carbon pellets needed to adsorb half the \(^{211}\text{Pb} \) emitted by the \(^{223}\text{Ra} \) source through its decay progeny, and \( A \) is the maximum activity the carbon pellets can adsorb with an unlimited mass of pellets.

To measure the \(^{219}\text{Rn} \) outgassing from a liquid sample, an aspiration cone was designed to fit over an open 5 mL vial with a nozzle that fits down into the vial just a few millimeters above the surface of the liquid. Fig. 3 shows a computer-aided design (CAD) cutout drawing and some photos detailing the design of the liquid aspiration cone. To measure the amount of \(^{219}\text{Rn} \) outgassing, a stock solution of about 30 kBq mL\(^{-1} \) of \(^{223}\text{Ra} \) was prepared. Three 5-h aspirations were done, with \(^{223}\text{Ra} \) liquid volumes of 1, 2, and 3 mL filled from the stock solution resulting in about 30, 60, and 90 kBq \(^{223}\text{Ra} \) liquid sample aspirations. The carbon pellets from the first air filter were collected in a 20 mL vial, and \(^{211}\text{Pb} \) spectra were acquired for 4 h in an HPGe detector. The long 4 h energy spectra acquisition was needed to collect as high statistics as possible for the 36.1 min \(^{211}\text{Pb} \) half-life without collecting too much background. The rate calculation takes into account the half-life of \(^{211}\text{Pb} \) and is decay corrected to the time the \(^{223}\text{Ra} \) source was removed from the aspiration hose.

As a test of the liquid aspirator cone, a few microliters of \(^{223}\text{Ra} \) was placed on a 5 × 5 mm glass fiber filter and allowed to dry. The activity of this dry \(^{223}\text{Ra} \) source was 63 kBq. The source was placed at the bottom of the 5 mL vial and was aspirated with the liquid aspiration cone for 5 h. The pellets of the carbon air filter were collected and placed in a 20 mL vial. A 90 min spectrum was collected on the HPGe detector.

To study the dispersion of \(^{219}\text{Rn} \) in ambient air, 5 × 5 mm glass fiber samples were prepared by soaking them with a few microliter drops of \(^{223}\text{Ra} \) and were set to dry. The samples had an average \(^{223}\text{Ra} \) activity of 27 kBq. A paper disk 8.6 cm in diameter was placed inside a 10-cm-diameter petri dish, and the \(^{223}\text{Ra} \)-laced 5 × 5 mm glass fiber filter was placed at the center of the petri dish on top of the 8.6-cm-diameter paper disk. The \(^{219}\text{Rn} \) outgassing from the 5 × 5 mm \(^{223}\text{Ra} \) sample was expected to contaminate the paper disk it was placed on. The petri dish had a 1.5-cm-high lip which contained the spread of the \(^{219}\text{Rn} \) outgassing contamination. To study the spread of contamination beyond the 10 cm diameter of the petri dish, a 24 × 19 cm sheet of paper was set down and a 5 × 5 mm \(^{223}\text{Ra} \) source was placed on its center. Fig. 4 shows the setup of one of the exposure tests in which two 24 × 19 cm sheets of paper were placed down, side by side. On one sheet, a single 5 × 5 mm \(^{223}\text{Ra} \) source was placed on its center. On the other sheet, three petri dish exposure setups were placed. A cardboard box was placed over the two 24 × 19 cm sheets to minimize any ambient airflow over the \(^{223}\text{Ra} \) sources for the 3 h exposure period.

After the exposure time elapsed and the \(^{219}\text{Rn} \) contamination distribution reached secular equilibrium, the

**Fig. 3.** This figure details the design of the 5 mL vial aspiration cone. Panel (a) is a CAD cutout showing in blue the 5 mL vial and in grey the aspiration cone with the nozzle which fits inside the vial to ensure proper airflow needed to aspirate any \(^{219}\text{Rn} \) outgassing from the \(^{223}\text{Ra} \) solution in the vial (online version in color). Panel (b) shows the 3D-printed aspiration cone and the 5 mL vial used to hold the \(^{223}\text{Ra} \) solution. Panel (c) shows the underside of a petri dish showing how the nozzle fits inside the vial. Panels (d) and (e) show the setup used to aspirate \(^{219}\text{Rn} \) from \(^{223}\text{Ra} \) solution.
$5 \times 5 \text{ mm}^{2}\text{Ra}$ source samples were removed and placed in individual 20 mL vials. The 8.6-cm-diameter paper disk samples were removed from the bottom of the petri dish and placed in a cartridge containing PSP autoradiograph plates, as were the two 24 cm paper sheets with each sheet placed in its own cartridge. The autoradiograph plates were exposed for 30 min. In order to prevent the plate from being contaminated, a 12.5-$\mu$m-thick sheet of Melinex (Melinex S 0.5 mil; Tekra, New Berlin, Wisconsin, US) was placed between the plate, the paper disk samples, and the 24 cm sheets. The 12.5-$\mu$m-thick Melinex sheet was tested to ensure that alpha particles from the decay of $^{223}\text{Ra}$ pass through the sheet, ensuring that the exposure of the autoradiograph plates was due mostly to the energy deposition of the alpha particles. After the 30 min exposure, the paper disks and 24 × 19 cm sheets were removed from the cartridge and placed in 20 mL vials, and the $^{211}\text{Pb}$ activity was measured using the microdose calibrator. The $5 \times 5 \text{ mm}^{2}\text{Ra}$ samples were also measured in the microdose calibrator. The autoradiograph plates were developed to generate image distributions of the $^{211}\text{Pb}$ contamination resulting from the outgassing of $^{219}\text{Rn}$ from the $^{223}\text{Ra}$ sources.

To measure the $^{219}\text{Rn}$ outgassing from murine tissue samples, athymic female nude mice (Ncr-nu/nu, National Cancer Institute, Frederick, Maryland, US) were injected intraperitoneally or intravenously via the tail vein with $^{223}\text{Ra}$.
and then euthanized (via CO₂ inhalation) at 30 min post ²²³Ra injection, at which time the organs were harvested. The organs were placed on 12.5-μm-thick Melinex sheets cut to the size of the organ and then placed in the center of 8.6-cm-diameter paper disks, which sat at the bottom of the 10-cm-diameter petri dish. This ²¹⁹Rn petri dish exposure setup is identical to the 5 × 5 mm ²²³Ra sample described above except that the sample replaces the 5 × 5 mm glass fiber ²²³Ra sample. The Melinex sheet placed between the organ and the paper disk is needed to keep the ²²³Ra in the organ tissue from contaminating the paper disk.

To measure the ²¹⁹Rn outgassing from the mouse carcass, a 14 × 6 cm rack was 3D printed. The rack was placed at the center of a 12 × 19 cm sheet of paper, and the mouse was placed on the rack in prone position with its open chest cavity placed downwards allowing any ²¹⁹Rn outgassing to fall onto the 24 × 19 cm sheet of paper.

Two sets of tissue outgassing experiments were performed. In the first one, 111 kBq of ²²³Ra was injected IP, and the kidney, spleen, muscle, and femur were placed in the petri dish to measure the ²¹⁹Rn outgassing. In the second experiment, 111 kBq of ²²³Ra was injected IV into one mouse, and its liver, kidney, spleen, muscle, and femur were exposed in petri dishes. Two other mice were injected, one with 37 kBq and the other with 9.3 kBq. The three mice carcasses were placed on racks sitting at the center of 12 × 19 cm sheets of paper exposing the sheets to ²¹⁹Rn outgassing.

All tissue and carcass exposures were for 3 h, and the exposed sheets were developed in the autoradiograph cassettes for 30 min. After the 30 min autoradiograph exposure, the paper disk and sheets were put in 20 mL vials, and ²¹¹Pb activity levels were measured in the microdose calibrator. Fig. 5 shows the setup of the tissue exposure experiment.

RESULTS

Fig. 6 shows plots of the ²²³Ra and ²¹¹Pb energy spectra acquired on the HPGe detector where the ²¹¹Pb sample was collected using the dry source aspiration method. These plots show that a nonmeasurable fraction of ²²³Ra escapes the glass fiber filter by noting the absence of any ²²³Ra gamma emission photopeaks in the ²¹¹Pb energy spectra. Fig. 7 shows the plots related to ²¹¹Pb capture in a carbon air filter when aspirating a dry ²²³Ra glass fiber source.

Fig. 5. Photos showing the tissue outgassing experimental setup. Panel (a) shows five different tissues: liver, kidney, spleen, femur (from left to right on the top row), and muscle (in the center bottom). Panel (b) is a closeup of the liver tissue. Panel (c) show the three mice carcasses resting on the 3D-printed frame above the paper. Panel (d) shows a closeup of the frame and how it is displaced from the surface of the paper sheet allowing for ²¹⁹Rn to outgas onto the paper sheet. Panel (e) shows the cart and the boxes covering each of the petri dishes (top shelf) and the mouse carcass (middle shelf). Panel (f) shows the autoradiograph of the ²¹¹Pb exposure from the mouse carcass on the left and the liver tissue on the right. Panel (g) shows the autoradiograph ²¹¹Pb exposure of the kidney, spleen, and muscle.
Fig. 7a plots the $^{211}$Pb activity as a function of the carbon pellet mass from four carbon filters placed in series along the vacuum hose. The data were fit with eqn (3), and the mass of carbon pellets needed to adsorb half the $^{211}$Pb is $2.3 \pm 0.1$ g. A single air filter contains about $4.6$ g of carbon pellets. Therefore, the capture efficiency of a single carbon air filter is about $74\% \pm 1\%$ for $^{211}$Pb. Fig. 7b plots the fractional $^{211}$Pb activity captured relative to the $^{223}$Ra activity in the dry paper filter being aspirated as a function of aspiration time. This plot graphs the rate at which the $^{211}$Pb being captured in the air filter reaches a plateau of maximum activity. From the fit of the data in Fig. 7b to eqn (3), the time it takes for the $^{211}$Pb to reach one-half of its plateau of maximum activity rate is $32 \pm 2$ min. Fig. 7c summarizes the total capture of $^{211}$Pb relative to the $^{223}$Ra activity in the dry paper filter being aspirated broken down by component. The total $^{211}$Pb captured averaged $51\%$, ranging from $30.8\%$ up to $81\%$. The carbon pellets captured an average $45\%$, ranging from $28.25\%$ up to $77.49\%$.

The $^{223}$Ra activity measurements in the 1, 2, and 3 mL liquid sample solutions were $30.1$ kBq, $57.1$ kBq, and $81.4$ kBq, respectively. From the HPGe energy spectra, the 1 and 2 mL liquid aspirations had negligible $^{211}$Pb activity: the 1 mL aspiration generated $600$ Bq ± $600$ Bq of $^{211}$Pb activity, and the 2 mL liquid aspiration generated $650$ Bq ± $430$ Bq of $^{211}$Pb activity. The 3 mL aspiration generated $710 \pm 240$ Bq of $^{211}$Pb activity. The upper limit on $^{219}$Rn outgassing from the liquid sample is $0.9\% \pm 0.3\%$. In contrast, the $66$ kBq dry paper source generated $32$ kBq of $^{211}$Pb activity or $48\% \pm 2\%$ of $^{223}$Ra activity. Fig. 8 displays plots of the $^{211}$Pb spectra between the energy of $340$ keV and $435$ keV for the sample collected from the dry source and the 3 mL liquid source.

The autoradiograph results of the $5 \times 5$ mm dry $^{223}$Ra source exposure can be seen in Fig. 4. Just a subset of the autoradiographs is shown, but it gives one a clear picture of the $^{211}$Pb contamination distribution resulting from the $^{219}$Rn outgassing from the $^{223}$Ra source. Fig. 4e is the autoradiograph of three exposed paper disks placed at the bottom of a petri dish with a $^{223}$Ra source placed in its center and the adjacent sheet placed under the three petri dishes. The autoradiograph of the paper disks
shows that the $^{211}\text{Pb}$ is mostly contained inside the petri dish, even though the top of the petri dish was removed during the 3 h exposure time. The 1.5 cm lip of the petri dish was enough to keep the bulk of $^{219}\text{Rn}$ inside the dish. The $^{223}\text{Ra}$ source placed on top of the sheet, which did not have the lip of the petri dish to contain the $^{219}\text{Rn}$, shows a much larger spread of contamination, even “seeping” between the petri dishes. This can be seen with careful inspection of the autoradiograph of the 19 × 24 cm paper sheet, which was placed below the petri dishes.

Fig. 9 shows radial profile plots of the autoradiographs from one of the disks placed inside a petri dish and of the two exposures of the $^{223}\text{Ra}$ source placed at the center of the 19 × 24 cm paper sheet. The 95% contamination spread for the source in the petri dish is 19 mm. For the two-sheet exposures, the radial length of the 95% contamination spread is 50 mm and 78 mm.

From the activity measurements of the exposed paper disks and sheets, which were made in the microdose calibrator and by drawing regions of interest on the autoradiographs which encompassed either the whole disk or the whole sheet and integrating the photostimulated luminescence recorded by the PSP plates, a PSL-to-Bq conversion factor of $(4.07 \pm 0.12) \times 10^{-3}$ Bq PSL$^{-1}$ was measured. The average amount of $^{211}\text{Pb}$ contamination per unit $^{223}\text{Ra}$ activity was measured to be 31% ± 4% for 10 exposed paper disks. The two sheets had contamination levels of 38% and 26%.

The autoradiograph images of the tissue and carcass samples are found in Fig. 5. There were two sets of tissue samples. One mouse had an IP injection and the other had an IV injection. Regions of interest were drawn on the autoradiographs to measure the $^{211}\text{Pb}$ activity levels caused by the outgassing of $^{219}\text{Rn}$ in the tissue samples and mice carcasses. The $^{223}\text{Ra}$ activity of the harvested organs was measured in the microdose calibrator. The results of the measurements are tabulated in Table 2. The carcasses used to measure the $^{219}\text{Rn}$ outgassing from the chest cavity all had IV injections. The carcass of the mouse which had an IP injection was not used to measure the $^{219}\text{Rn}$ outgassing from the chest cavity; therefore, there is no data for that.

![Fig. 8. Comparison of $^{211}\text{Pb}$ spectra collected from a dry and liquid sample of $^{223}\text{Ra}$. Panel (a) is the $^{211}\text{Pb}$ spectrum collected from a dry $^{223}\text{Ra}$ source; panel (b) is one collected from the $^{223}\text{Ra}$ solution. Both the dry and liquid sources contain about 111 kBq of $^{223}\text{Ra}$. The dry source was aspirated for 3 h while the liquid source was aspirated for 5 h. The part of the energy spectra shown shows three peaks, the 351 keV $^{211}\text{Bi}$ gamma emission, and the 404 keV and 427 keV $^{211}\text{Pb}$ emission peaks. The $^{211}\text{Pb}$ activity rate is measured in part from the 404 and 427 keV peaks. From the noise levels of the baseline in the spectrum in panel (b), one can visually see how much less $^{211}\text{Pb}$ is aspirated from a $^{223}\text{Ra}$ solution than from a dry source.](image1)

![Fig. 9. Profile distribution plots of $^{211}\text{Pb}$ contamination from the $^{223}\text{Ra}$ source. The profiles were measured from the autoradiograph images of the paper disk and sheet exposed to the 5 × 5 mm $^{223}\text{Ra}$ glass fiber filter source. Panel (a) is the profile data in units of PSL, the units defined by the autoradiograph device, which is linearly proportional to the integrated energy deposited in the autoradiograph plates during the exposure time. Of the 10 paper disks exposed inside petri dishes, only 1 is shown in green (online version in color), which is a typical profile distribution. Two paper sheet exposures were made in which each showed a slightly different distribution due to the subtle airflows inside the cardboard box placed over the sheets during the 3 h sheet exposure period. The profile distribution of the source on sheet 2 (red; online version in color) had greater dispersion due to possible greater airflow inside the box. Note that the airflow inside the cardboard box is very small, but the dispersion measurement is very sensitive to the smallest of air disturbances. Panel (b) is an integrated profile as a function of distance from the source normalized to unity. This provides a measure of the extent of the contamination from the $^{223}\text{Ra}$ source.](image2)
From the data in Table 2, it is shown that there is a difference between the outgassing levels when doing an IP injection rather than an IV injection. The outgassing levels were measured to be up to 10.1% ± 0.4% of $^{223}$Ra in the spleen for the mouse which had the IP injection, with the muscle at 9.4% ± 0.7% and the kidney at 3.8% ± 0.2%. This compares to less than 1% for all organs harvested from the IV-injected mouse. The outgassing from the chest cavity of the carcass was 0.028% ± 0.003%.

### DISCUSSION

The first observation is that working with dry $^{223}$Ra poses a much larger contamination risk than working with $^{223}$Ra in solution. This is seen by the difference in $^{211}$Pb collection percentage between the dry and liquid $^{223}$Ra sources, which are 51% ± 21% and 0.9% ± 0.3%, respectively; a factor of about 50. The low outgassing is because $^{219}$Rn is soluble in water (230 mL L$^{-1}$) (Keith et al. 2012), thus trapping the gas and lowering the outgassing rate by more than an order of magnitude.

When working with mice, the level of $^{211}$Pb contamination measured by the autoradiograph studies (Fig. 5) showed different results for the two injection methods used. The IP-injected mice had $^{219}$Rn outgassing levels up to 10.1% ± 0.4%, while the IV-injected mice had levels below 1%. Note that when exposing the tissue samples to the paper disks in the petri dishes for 3 h, the surface of the tissue samples dried to some extent. Visual inspection of the surface of the organ tissue indicated some drying had occurred during the 3 h exposure time. Therefore, the IP-injected organ tissue samples showing as high as 10% $^{211}$Pb contamination are probably an overestimation, considering that one handles the tissue samples while they are moist during and shortly after they are harvested.

The outgassing from the mouse carcass was measured only for the IV-injected case. The low levels of outgassing could be related to the IV injection, similar to the low levels of outgassing seen in the IV-injected organ samples.

There is a large difference between IP and IV outgassing results of a factor of 50. There is no hypothesis to offer that might explain it. Further research is needed to find out the underlying reason.

One model of $^{210}$Rn outgassing that comes to mind is something akin to condensation vapor coming off dry ice. Because of the large atomic weight of $^{210}$Rn, after it escapes from the material that $^{223}$Ra is in, it tends to stay low and gravitationally pulled down. This is evident from a few trial runs at collecting $^{219}$Rn from a dry $^{223}$Ra source in a vial. The first cone design used to aspirate $^{219}$Rn from $^{223}$Ra in a vial failed. The design was simply a cone, which was placed over the top of an uncapped vial. There was plenty of airflow at the vial top opening, but the carbon air filter in the aspiration hose didn’t pick up any $^{211}$Pb. Then a nozzle was added to the cone, so when the cone was placed over the uncapped vial the nozzle would enter the opening and aspirate air from inside the vial. This design was able to accumulate a large sample of $^{211}$Pb in the carbon air filter. This was a clear indication that for the most part $^{219}$Rn outgassing from $^{223}$Ra stayed inside the vial. But once one creates airflow close to the source of the $^{223}$Ra, then one can easily affect the movement of the $^{219}$Rn. The dry 5 × 5 mm $^{223}$Ra source exposure of the paper disks inside the petri dish is another example. The 1.5 cm lip of the petri dish was sufficient to contain the spread of the radon as it was seen that there was very little activity on the paper sheet placed below the petri dishes shown in the autoradiograph exposure of the sheet (Fig. 4.)

In the Introduction, the US NRC inhalation dose limits were briefly discussed for $^{223}$Ra, $^{219}$Rn, and $^{211}$Pb. Because of the short half-life of $^{219}$Rn compared to $^{223}$Ra, a 1 h continuous inhalation of 37 kBq of $^{219}$Rn gave a whole-body effective dose exposure of 0.27 mSv, which is on the order of 200 times less than the US NRC ALI of 50 mSv. This makes $^{219}$Rn nowhere as dangerous as $^{223}$Ra. This is especially true when working with doses near or less than 37 kBq, which is typical for preclinical studies, and if any exposure to inhaled $^{219}$Rn happened its duration would be limited.

### Table 2. Table detailing the outgassing measurements from the mouse tissue samples.

| Mouse # | Organ   | $^{223}$Ra (Bq) | $^{211}$Pb (Bq) | % Emission |
|---------|---------|-----------------|-----------------|------------|
| 1—IP    | Kidney  | 1,160 ± 30      | 44.40 ± 1.3     | 3.8% ± 0.2%|
| 1—IP    | Spleen  | 1,560 ± 40      | 158 ± 5         | 10.1% ± 0.4%|
| 1—IP    | Muscle  | 144 ± 10        | 13.4 ± 0.4      | 9.4% ± 0.7%|
| 1—IP    | Femur   | 43.6 ± 10       | 0.0482 ± 0.0014 | 0.11% ± 0.03%|
| 2—IV    | Liver   | 58,200 ± 1,300  | 119 ± 4         | 0.204% ± 0.006%|
| 2—IV    | Kidney  | 1,140 ± 180     | 1.07 ± 0.03     | 0.09% ± 0.02%|
| 2—IV    | Spleen  | 6,400 ± 220     | 2.96 ± 0.09     | 0.046% ± 0.002%|
| 2—IV    | Muscle  | 151 ± 180       | 0.0842 ± 0.0025 | 0.06% ± 0.06%|
| 2—IV    | Femur   | 28.6 ± 180      | Unmeasurable    | Unmeasurable|
| 2—IV    | Carcass | 33,000 ± 3,000  | 9.3 ± 0.3       | 0.028% ± 0.003%|

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One should note that the calculation is very simple and does not include factors such as treating the airborne $^{219}\text{Rn}$ and its progeny as aerosols or taking into account breathing rates, dilution factors due to activity concentrations in air, the total air volume in the lab, etc. A more comprehensive treatment of inhalation exposure of $^{219}\text{Rn}$ was done by Stabin and Siegel (2015), in which effective dose was calculated for a spill of 10 MBq of $^{223}\text{Ra}$ from which a person was exposed to the $^{219}\text{Rn}$ emissions from the $^{223}\text{Ra}$ spill for half an hour, the estimated time to clean up the spill. In this work, Stabin and Siegel estimated the effective dose to be $2.8 \times 10^{-3}$ mSv. If we plug in numbers scaled to the 1 h exposure of 37 kBq $^{223}\text{Ra}$, one would get about $2 \times 10^{-5}$ mSv.

The situation in which one should be most careful is in handling the source vial. $^{223}\text{Ra}$ is obtained from Oak Ridge National Laboratory in the form of dry $^{223}\text{Ra}$ nitrate caked at the bottom of a glass vial. The amount ordered is typically in the tens of MBq. Since the outgassing levels for dry $^{219}\text{Rn}$ are around 50% and could be higher for dry $^{223}\text{Ra}$ caked at the bottom of a glass vial, handling of the source vial and any purification procedures should be carried out with the utmost caution. For example, if one were to work with a 37 MBq $^{223}\text{Ra}$ source vial performing a purification procedure that takes 1 h, the worst-case upper limit inhaled dose could reach 268 mSv, assuming 100% $^{219}\text{Rn}$ outgassing and direct inhalation. This is well beyond the 50 mSv US NRC annual dose limit.

The main goal of the study presented herein was to understand the physical characteristics of $^{219}\text{Rn}$ dissemination from a $^{223}\text{Ra}$ source leading to $^{211}\text{Pb}$ contamination. What one learns from this study should be used as input to more comprehensive dose exposure studies as have been done by Stabin and Siegel (2015). For example, one datum point learned is that in a lab which has no airflow, $^{219}\text{Rn}$ does not diffuse through the air but is influenced by gravitational forces and will concentrate on the surface where a $^{223}\text{Ra}$ solution was spilled. To spread the $^{219}\text{Rn}$ gas, one needs forced air movement which will complicate the inhalation exposure model. Another datum point is that if the spilled $^{223}\text{Ra}$ was in the form of a solution, then on the order of 1% of the $^{219}\text{Rn}$ gas will actually escape from the solution. But on the other hand, if the solution dries, then the amount of outgassing can go as high as 50% of the spilled $^{223}\text{Ra}$ activity. So liquid vs. dry models should be explored. The work done by Stabin and Siegel (2015) focused on the radiation safety hazard to a lab worker handling a dose of $^{223}\text{Ra}$ dichloride for therapeutic use. Applying what has been learned from this study to a comprehensive and detailed radiation dose exposure model for preclinical studies and the handling of source vials of $^{223}\text{Ra}$ dichloride that contain up to 100 MBq of activity, which in turn are purified possibly involving evaporation steps, is best addressed in a separate publication.

**CONCLUSION**

An extensive study of $^{219}\text{Rn}$ outgassing from $^{223}\text{Ra}$ in dry, liquid, and tissue samples was performed. The study measured relatively high levels of outgassing in dry $^{223}\text{Ra}$ samples (51% ± 21%), very small levels of outgassing in liquid $^{223}\text{Ra}$ samples (0.9% ± 0.3%), and a noticeable difference in tissue outgassing depending on the injection type, being either IP (10.1% ± 0.4%) or IV (<1%). The outgassing kinetics suggests the $^{219}\text{Rn}$ gas will disseminate up to 8 cm under controlled quiescent airflow conditions. The 1.5 cm lips of the petri dishes used in the paper disk exposure experiments were high enough to contain the spread of the $^{219}\text{Rn}$ gas. Further aspiration tests indicate that the $^{219}\text{Rn}$ gas will be trapped in the bottom of an open vial.

The use of $^{223}\text{Ra}$ in preclinical studies poses minimal health risk due to $^{219}\text{Rn}$ outgassing using injected doses in the 37 kBq range. One should ensure that $^{223}\text{Ra}$ dichloride is prepared in a proper ventilated hood when handling amounts in the 37 MBq range, which is the typical amount in a source vial.

Even though exposure to the inhalation of $^{219}\text{Rn}$ contributes negligibly to one’s yearly dose limit of 50 mSv when using it to perform biodistributions, it is important to understand the generation and dissemination of $^{219}\text{Rn}$ from $^{223}\text{Ra}$ from a radiation health and safety perspective.

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