Transfer Rates of $^{225}$Ac to Exhaust Air, Surface, and Waste Water under Chemical Operations

Tomoo YAMAMURA$^{1,2)}$, Kenji SHIRASAKI$^1$, Hidetoshi KIKUNAGA$^3$, Kojiro NAGATA$^4$, Zi Jian ZHANG$^5$, Kohshin WASHIYAMA$^6$, Atsushi TOYOSHIMA$^7$, Takashi YOSHIMURA$^4$, and Atsushi SHINOHARA$^5$

$^1$ Laboratory of Alpha-ray Emitters, Institute for Materials Research, Tohoku University, Miyagi 980-8577, Japan
$^2$ Institute for Integrated Radiation and Nuclear Science, Kyoto University, Osaka 590-0494, Japan
$^3$ Research Center for Electron Photon Science, Tohoku University, Miyagi 982-0826, Japan
$^4$ Radioisotope Research Center, Institute for Radiation Sciences, Osaka University, Osaka 565-0871, Japan
$^5$ Department of Chemistry, Graduate School of Science, Osaka University, Osaka 560-0043, Japan
$^6$ Advanced Clinical Research Center, Fukushima Medical University, Fukushima 960-1295, Japan
$^7$ Division of Science, Institute for Radiation Sciences, Osaka University, Osaka 560-0043, Japan

Received Dec. 19, 2019; accepted Mar. 19, 2020

Actinium-225 is one of the most promising nuclides in the field of nuclear medicines for treatments of cancers, whereas the transfer rate of $^{225}$Ac during chemical treatments, required for the radiological protection of the radiation workers, has not been determined. In this study, firstly, the chemical operations and the chemical status required for dealing with $^{225}$Ac for nuclear medicines were selected, and secondly, the dispersal rate, the surface contamination, and the concentrations of radionuclides in the waste water of $^{225}$Ac were determined. The total dispersal rates were determined as low values ($2\sim4 \times 10^{-6} \, \text{h}^{-1}$) and high values ($2\sim4 \times 10^{-5} \, \text{h}^{-1}$), depending on the classes of operations, and that in the exhaust as $1 \times 10^{-7} \, \text{h}^{-1}$. These values are about an order of magnitude smaller than that of the “in surface” for normal chemical operations.

Key Words: Actinium-225, dispersal rate, chemical operations, DOTA, pH

[doi:10.12950/rsm.191219]

1. Introduction

Short-lived alpha-emitting radionuclides attract growing attentions as nuclear medicines because of their characteristics of the large LET (linear energy transfer) to neighbor cells and the short path length, which results in lethal damages if they are conveyed to tumor cells by DDS (drag delivery system) using the antigen-antibody recognition. Actinium-225 ($T_{1/2} = 9.92 \, \text{d}$), which emits four alpha particles in a series of decays, is one of the most promising nuclides for the targeted alpha therapy (TAT). Figure 1 shows the decay scheme of $^{225}$Ac including its ancestors from $^{233}$U alongside axis (rows) of atomic number (element). The downwards and the right-upwards arrows show the $\alpha$-decay and $\beta$-decay, respectively, with their thickness indicative of the yields of the decays. After the generation and the purification of $^{225}$Ac by the milking, the nuclides starting from $^{225}$Ac (surrounded by dashed box) are generated in the system.

In 2016, a remarkable therapeutic effect of $^{225}$Ac was proved by clinical results on a brief communication report$^1)$. By the treatments with $^{225}$Ac-PSMA-617, the widespread metastatic lesions of two patients under challenging clinical situations completely disappeared. This report prompted
researchers urgent and extensive studies on ²²⁵Ac nuclear medicines for practical applications. Actinium-225 is a nuclide in the natural decay series starting from ²³⁷Np, which is the missing parents in the present earth because of its short lifetime \((2.14 \times 10^6 \text{ y})\) compared to the age of the earth. At the present, ²²⁵Ac is practically generated by milking processes from the parent ²²⁹Th, which was extracted from the legacy ²³³U wastes produced in the neutron irradiation to thorium.

In the facilities for handling the radioisotopes and for administering the radiolabeled pharmaceuticals, the radioactivity concentrations in air and in exhaust gas of working rooms are regulated to be kept below a specified value. A factor which affects directly the radioactivity concentrations in air or in exhaust gas is the rate of dispersion and emanation from the radioactive materials used.

The dispersal rates are experimentally determined only for limited elements, nuclides, chemical forms, physical status, and experimental operations. The dispersal rates of radioisotopes under general operations were systematically determined and reported for 13 different nuclides and 16 different chemical forms².³. However, ²²⁵Ac has never studied from the point of view of the radiological protection up to the present. The ICRP recommendations describing the handling of unsealed radionuclides in hospitals and research institutes, published in 1964⁴ and in 1977⁵, gave no description on ²²⁵Ac. Recently, the radionuclides emitting γ-ray or β-ray have been used in the nuclear medicine, and discussed in terms of decontamination in such institutes⁶. Also, ²²⁵Ac had not been included in the nuclides for radioactivity measurement at regulatory release levels⁷, mainly because the nuclide is not produced in nuclear reactors.

To cover the emerging application of ²²⁵Ac to the nuclear

---

Fig. 1. Decay scheme of ²²⁵Ac including its ancestors from ²³³U alongside axis (rows) of atomic number (element), with their boiling point as a measure of the ease of vaporization. The energies (MeV)² in bold style indicate they are used in measurements.
medicines, the dispersion and the contamination accompanied by the treatment of $^{225}\text{Ac}$ are to be estimated. In terms of the chemical treatments in laboratories, unit operations required for the production and the purification, i.e. the milking process from $^{229}\text{Th}$, and the radiolabeling of the DOTA-linked antibodies are to be included, where DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) is a potential chelate ligand for $^{225}\text{Ac}$. Such unit operations required for the milking and the radiolabeling are depicted in Fig. 2. The procedures deal with several to tens of mL amount of $^{225}\text{Ac}$ as the source of contamination, under unsealed conditions. It also includes the centrifuge in the milking, voltex mixing in the labeling, and finally the washing for finalizing the processes. These chemical treatments accompany the partial transfer of $^{225}\text{Ac}$ to exhaust air and to the surface, which is required to be evaluated in terms of the radiological protection of the radiation workers.

The operations required for the chemical treatments of $^{225}\text{Ac}$ with their objectives in the laboratories are summarized in Table 1. Also, the table includes chemical status of $^{225}\text{Ac}$

**Table 1. Classification of chemical operations and chemical status encountered in dealing with $^{225}\text{Ac}$ for nuclear medicine, and studied in this report.**

| Classification | Entry   | Content                        | Objective                                      |
|---------------|---------|---------------------------------|------------------------------------------------|
| Chemical operation | 1 Stirring | Dissolution, Mixing            | Dissolution, Mixing                            |
|               | 2 Heating and Evaporation | Radio-labeling, Volume reduction, Crystallization Column separation, Addition, Titration | Radio-labeling, Volume reduction, Crystallization Column separation, Addition, Titration |
|               | 3 Dripping |                                  | Dryness, Crystallization, Removal of solvent   |
|               | 4 Standing |                                  | Extraction by resin                            |
|               | 5 Centrifuge |                                  | Extraction by resin                            |
|               | 6 Vortex mixing |                                  | Washing of tools and beakers                   |
|               | 7 Washing |                                  | Standard solution                              |
| Chemical status | i 0.05 M nitric acidic solution | Equilibrated with phosphoric acid | Equilibrated with phosphoric acid |
|               | ii pH 7 buffer solution |                                   | Labeled in MES$^1$ buffer solution            |
|               | iii DOTA complex solution |                                   | Labeled in MES$^1$ buffer solution            |
|               | iv solid nitrate |                                   | Labeled in MES$^1$ buffer solution            |

$^1$ MES: 2-(N-morpholino)ethanesulfonic acid
encountered in such treatments. The chemical status is typically composed of weak acidic solutions, pH 7 buffer solutions, labeled solutions, and solid products.

This study was planned to evaluate the dispersal rate, and the radionuclide concentrations in the waste water of $^{225}$Ac in chemical experiments by establishment of a standard experimental method. The dispersal rate was obtained for each chemical status, and for each experimental unit procedure summarized in Table 1. To obtain acceptable values of the dispersal rates for $^{225}$Ac, in addition to follow the precedent methodology demonstrated by Muto et al.21, various improvements in experimental components, and equipments developed in the four decades were introduced. Typical substitutions are the filter holder, and the cylinder whose inside is lined with films. The former one (the filter folder) contributed the quantitative adsorption of iodine or actinium within compact mechanical structure with a smooth connection with cylinder. The latter one (cylinder and its liner films) enabled us in the easiest way to measure the dispersion onto surfaces. To check the validity of our data by comparison with the literature, the dispersal rates of $^{131}$I was adopted for the proof of our experiments prior to the $^{225}$Ac experiments.

To incorporate the ICRP Publication 60 (Recommendation 1990)8 into our domestic regulation system in Japan, the guideline for management of radioisotope concentrations in exhaust gas and waste water was published by the cooperative activities of the Japanese Society of Radiological Technology, and the Japanese Society of Nuclear Medicine Technology9. The dispersal rate of radioisotopes both in liquid or solid forms to air is specified as 0.01 against the maximum amount of radioisotopes used per day, regardless of the specifications of materials mentioned above. As the values were set uniformly with a margin on the safe side, the values have large margins for specific nuclides, chemical forms, or the methods adopted. In recent demand for handling of a large amount for medical applications, such uniform and overestimated values would impose the facilities a large redundancy in abilities of the radiation protection.

This manuscript reports the transfer of $^{225}$Ac observed in chemical treatments (Fig. 2) divided broadly into three categories. Firstly, the stirring, the evaporation by heating, the dripping, and the standing treatments were carried out, and transfer rate to the exhaust air and the surface were evaluated. Secondly, the centrifuge, and the Vortex mixing procedures were tested in the sample tubes, and the transfer or the leakage to the outer bag was checked. Thirdly, the washing of the beaker once used for storing $^{225}$Ac solution was carried out by monitoring the transfer to the rinses.

2. Experimental
2-1. Preparation of $^{225}$Ac solutions

The stock solutions of $^{229}$Th in 8 M HNO₃ (0.5 mL) was pointed to the top of the two-staged columns (Muromac S) filled with the anion-exchange resin (Muromac 1 × 8, 100–200 mesh). The eluted drops from the upper column were directly introduced to the lower column, whose eluted solution was collected (the solution-1). The connected columns were washed with 8 M HNO₃ with the volume of 3 mL, followed by the washing of the lower column with that of 3 mL, and the eluted were joined to the solution-1. The $^{229}$Th fraction was recovered by washing of the upper column with 2 M HCl of 10 mL, followed by washing with 5 mL of water. After the solution-1 was evaporated to dryness, 0.5 mL of 3 M HNO₃ was added to obtain $^{225}$Ra and $^{225}$Ac mixed solution. The solution was dripped on the extraction chromatography resin column (DGA-resin-branched, 50–100 μm, 2 mL cartridge, Eichrom Technologies, LLC, USA), followed by 6 mL of 4 M HNO₃, to remove and wash $^{225}$Ra. By back extraction with 10 mL of 0.05 M HNO₃, $^{225}$Ac without $^{225}$Ra impurity was obtained10,11, which was evaporated to nearly dryness, to which 20 mL of a desired acidic solution was added to obtain the $^{225}$Ac stock solution.

The preparation of the neutral MES buffer (pH 6.2) including $^{225}$Ac-DOTA complex was prepared by a method slightly improved from the literature12, where MES is the abbreviation of 2-(N-morpholinoo)ethanesulfonic acid. Once the evaporated $^{225}$Ac solution to dryness was dissolved again by adding 100 μL of 0.05 M HNO₃ the solution was mixed together with the aqueous solution 20 μL of 0.48 mg DOTA, and the aqueous solution 5 mL of 1 M ammonium acetate. Then, the solution was vigorously shaken at 40°C for half an hour by voltex mixing (1,500 rpm). The MES buffer was added to this solution to adjust the volume to 20 mL. All chemicals without radionuclides were purchased from FUJIFILM Wako Pure Chemical Corporation. Nitric acid of “Super Special Grade” was used. Mill-Q ultrapure water system (Millipore Corp., U.S.A.) was used for generating pure water.

2-2. Definitions of dispersal rates

During a certain experimental operation as illustrated by Fig. 2, the radioactivity ($A_{\text{max}}$) could be partly retained in the
experimental system \( (A_0^{\text{retained}}) \), but the others may be lost in waste water \( (A_0^{\text{ww}}) \) and in the environments by dispersion \( (A_0^{\text{dispersed}}) \), as eq. (1). The law of the conservation of mass is valid for the \(^{225}\text{Ac}\) activity by correcting the decay to the initial time. On the basis of eq. (1), the experimental system is defined as the \(^{225}\text{Ac}\) sample with containers such as beakers and sample tubes. Then, the ratio of the activity lost in dispersion \( (\eta_{\text{total}}) \) had been recognized as that it increases with the time of a certain operation \( (t_{\text{operation}}) \), as given by eq. (2). The evaluation of \( \eta \) follows the conventional methodology, where it is determined in the experiments for an hour\(^2\), on the assumption that the amount of transfers is proportional to the time required for the operation. Here, the total dispersal rate could be given by eq. (3), where the total dispersal rate is broken down into two parts of dispersal rate in exhaust \( (\eta_{\text{exhaust}}) \), and that in surface contamination \( (\eta_{\text{surface}}) \).

\[
A_0^{\text{total}} = A_0^{\text{retained}} + A_0^{\text{dispersed}} + A_0^{\text{ww}} \quad (1)
\]

\[
A_0^{\text{dispersed}} = \eta_{\text{total}} \cdot t_{\text{operation}} \quad (2)
\]

\[
\eta_{\text{total}} = \eta_{\text{exhaust}} + \eta_{\text{surface}} \quad (3)
\]

Under the condition where the identical geometry is applied during the investigation, the above relationships can be broken down into different forms. Experimentally, radioactivity \( A \) is related directly to the count rate in cps \( n \) by eq. (4), where \( \epsilon_{\text{detection}} \) is the detection efficiency, and \( \epsilon_{\text{branch}} \) is the branching ratio in the observed energy. Then the eqs. (1) and (2) can be transformed to eqs. (5) and (6), respectively.

\[
A = \frac{n}{\epsilon_{\text{branch}} \cdot \epsilon_{\text{detection}}} \quad (4)
\]

\[
n_{\text{total}}^0 = n_{\text{retained}}^0 + n_{\text{dispersed}}^0 + n_{\text{ww}}^0 \quad (5)
\]

\[
n_{\text{dispersed}}^0 = \eta_{\text{total}} \cdot t_{\text{operation}} \quad (6)
\]

The forms of eqs. (5) and (6) are equivalent to the former eqs. (1) and (2) under the above-mentioned condition. However, one advantage could be the explicit description of the precision of the activities which is quite important for the evaluation of the dispersion. In other words, only extraordinary small or negligible amount of \(^{225}\text{Ac}\) atoms transfers, and only a few to several counts are obtained in many cases even for accumulation periods. Also, during the present study, by using the \(^{225}\text{Ac}\) obtained by a single milking generation, many experiments and much more measurements should be finished within a small period governed by the short decay lifetime. Therefore, it is better to deal with the obtained counts directly than to deal with the activity in Bq. In the following section, the activity \( A \) can be substituted by using \( n \) whenever the relative amounts are concerned.

2-3. Apparatus for collection of dispersed radionuclides

The measurement system for the dispersal rate (Fig. 3) is mainly constructed within a glovebox system, which is equipped with a feed-through pipeline. Through the feed-through pipeline, the air was evacuated by an aspirator (LV-40BW, SIBATA Scientific Technology Ltd., Japan). The sampling part is composed of the iodine sampler holder (RI-55 type, SIBATA Scientific Technology Ltd., Japan), whose inlet part is modified to connect a cylinder made with acryl (the inside diameter is 70 or 41 mm; the length is 468 mm). Inside of the acryl-made cylinder is tightly covered by a PEN sheet.

In this study, the reproducibility of our apparatus was checked by using \(^{131}\text{I}\), and by the comparison with the literature value\(^2\). Iodine-131 (74 MBq), purchased from PerkinElmer Inc., was dissolved in 1 mL of 0.1 M NaOH. By sampling several mL of the solution to a beaker, followed by adding pH 7 buffer solution. After the stirring the sample solution at 500 rpm for 1 hour, \( \gamma \) spectrometry of all the samples (a glass filter, active carbon filters, O-rings, cut sheets of PEN film) were carried out at 365 keV (yield: 81.7%). Also, the weight decrease of the sample solution was measured.

For the \(^{131}\text{I}\) experiments the sample holder was used "as purchased" with the iodine sample filters. For the \(^{225}\text{Ac}\) experiments, in place of the iodine filters, the two sheets of Resolve PTFE filters (RP-50-47PTFE3, Eichrom Technologies, LLC, USA), which designed for the particle sampling (recovery yield > 80%) and the \( \alpha \) spectroscopy (resolution < 60 keV), are installed in layer.

The dispersal rate during chemical operations were determined as followings. The stirring and the evaporation by heating were carried out by using a magnetic stirrer, on the top of which a rubber heater was placed on a heat insulation board. For the heating, the temperature of the side surface of the beaker was maintained to 80°C for an hour. The dripping the \(^{225}\text{Ac}\) solutions was carried out at the speed of 0.3 g/min by controlling with a syringe pump from the height of ca. 50 cm to the empty beaker placed. For the dripping experiment, the acrylic cylinder has a hole to place the dripping nozzle.
2-4. \(\alpha\) and \(\gamma\) spectrometry

The spectrometry measurements were done in two ways. Firstly, it was done just after the experiments, and secondly after the attainment of the radioactive equilibrium. Experimental detections of \(^{225}\text{Ac}\) and its daughters were carried out by \(\alpha\) spectroscopy. In the detection of the samples from centrifuge and vortex mixing experiments, \(\gamma\)-ray spectrometry was applied. In both cases, measurements and the analysis of the radioactivities of the daughter nuclides were underwent after an enough period for radioactive equilibrium. The emission energies of the nuclides, used for the spectrometry, in the series are described in Fig. 1.

The alpha spectrometer (SOLOIST, ORTEC) with a Si detector (ORTEC, BU013-150-300) was calibrated by using an AMR33 (Amersham) standard source. In this study, all samples for the alpha spectrometry are measured under the identical geometry between the detector and the sample in the spectrometer chamber. On the basis of eq. 4, \(\epsilon_{\text{detection}}\) was determined as 0.2035. The activity values in Bq are calculated and shown on the basis of the \(\epsilon\) value, whereas the count rate can be used in the evaluation of the dispersal rate because of the identical geometry through the study. The detection limit of the \(\alpha\) spectrometry was evaluated by assuming one count within the described accumulation time, and indicated in tables by using the inequality symbol (“<”).

The germanium semiconductor spectrometer used in gamma spectrometry is GMX30P4-70 (ORTEC-AMETEK). The energy calibration was carried out, and the detection efficiency was determined, by using an \(^{152}\text{Eu}\) standard source. The detection efficiency was determined by eq. 4, under the identical geometry between the detector and the samples (folded within 50 \(\times\) 50 mm size if the size is larger) as \(\epsilon_{\text{detection}}\). For the centrifuge, the vortex mixing, and washing experiments, the samples were placed at the distance of 3 cm from the top of the detector.

2-5. Determining dispersal rates of exhaust and of surface

The dispersal rate was determined by the alpha spectrometry of the PTFE filters and the PEN films. The procedures adopted include: Just after the end of the sampling, the sampling part was disassembled to parts including the PTFE filters and the sheet of the PEN film. The PEN film was cut into three disks with the diameter of 40 mm from the upper, the middle, and the lower parts of the cylinder (Fig. 3). The PTFE filters and the disks of the PEN films were set into the chamber of the alpha spectrometer, and the measurements were started.
The dispersal rate in exhaust ($\eta_{\text{exhaust}}$) could be reasonably approximated by eq. (7), where $\eta_{\text{Filter-L}}^{\text{exp}}$ is the dispersal rate determined experimentally by using the PTFE filter (Filter-A) as the first stage filter, and $\epsilon_{\text{collection}}$ is the collection efficiency of the nuclide by the sheet.

$$\eta_{\text{exhaust}} = \eta_{\text{Filter-L}}^{\text{exp}} / \epsilon_{\text{collection}} \ldots (7)$$

Also, the dispersal rate in surface contamination ($\eta_{\text{surface}}$) is related to eq. (8), where $\eta_{\text{Filter-L}}^{\exp}$ is the dispersal rate determined experimentally by using the PEN film (whole area is $S_0$), and the disk for measurement (the disk area is $S_1$) is sampled ($S_0 / S_1 = 8.19$, Fig. 3).

$$\eta_{\text{surface}} = \eta_{\text{Filter-L}}^{\exp} \cdot \frac{S_0}{S_1} \ldots (8)$$

The value $\eta_{\text{surface}}$ is overestimated because of using the activity of the film cut at the lowest part ($\eta_{\text{Filter-L}}^{\exp}$). However, the value $\eta_{\text{Filter-L}}^{\exp}$ was used as $\eta_{\text{surface}}$ to preserve a margin on the safe side.

The collection efficiency ($\epsilon_{\text{collection}}$) is derived from the counts of the two successive filters. By assuming the activity of 225Ac in the exhaust is $A_0$, the collected activity on the Filter-A as $A_1 = \epsilon_{\text{collection}} A_0$, and that on the following Filter-B as $A_2 = \epsilon_{\text{collection}} (1 - \epsilon_{\text{collection}}) A_0$. Therefore, the collection efficiency is given by eq. (9). Though the efficiency could be common to a certain couple of the nuclide (225Ac) and the filter, we use a different efficiency determined in each system for the consideration on the safe side.

$$\epsilon_{\text{collection}} = 1 - \frac{A_2}{A_1} \ldots (9)$$

2-6. Determining contamination under centrifugal separation and vortex mixing

The dispersal rate of the centrifugal separation and the vortex mixing of the solutions were determined according to the procedures described below. A PP tube with volume of 1 mL was used as a container of 0.05 M nitric acid with 225Ac, and sealed in a different PE bags. The centrifuge was carried out by setting the PP tube with the bag, respectively, to a small centrifuge (Putchimar8, Waken b tech, Co. Ltd., Japan), and done for 6 minutes at the speed of 6,000 rpm. The mixing was carried out by setting the PP tube in the bag to a vortex mixer (Vortex-Genie 2, Scientific Industries, Inc., U.S.A.) at the speed of 8/10 of the maximum speed. After each of the centrifuge and the vortex mixing experiments, three bags for the three samples for each procedure were collected and subjected to the $\gamma$ spectrometry. Their $\gamma$ spectra were obtained, and the activities for 225Ac at 150 keV, 221Fr at 218 keV, and 213Bi at 440 keV were determined before ($A_0$) and after the centrifuge ($A_1$) or the mixing ($A_2$).

2-7. Determining concentrations of radionuclides in waste water

The concentrations in the waste water was determined by the $\gamma$ spectrometry according to the procedures described below. The beaker used for storing 225Ac solution was rinsed with 1 mL of ethanol 6 times, and the rinse liquid was collected in a PP tube. From the liquid collected in the PP tubes, a sample for the $\alpha$ spectrometry was prepared by the evaporation to dryness. For the complementary purpose, the $\gamma$ spectrometry was applied to determine radioactivities on the beaker after the rinse, the pipet tip used for rinse, and the magnetic stirring chip used to prepare the aqueous solutions. The geometry between the detector and the sample to assure the reproducibility was as follows. The PP tubes with liquid was standing at 17 mm apart from the top of the detector with the center of the gravity was located on the center of the detector cylinder. The beaker was located at 17 mm apart with the center axis was identical to that of the detector cylinder.

3. Results and discussion

3-1. Dispersal rate of $^{131}$I

The dispersal rate of $^{131}$I (Tables 2 and 3) shows the appropriate consistency with the literature values$^2)$. In detail, the dispersal rate of $\eta_{\text{exhaust}} = 9.6 \times 10^{-5}$ h$^{-1}$ (Table2) is slightly larger but comparable to the literature value from $(1.7 \pm 0.98) \times 10^{-5}$ (Na$^{125}$I) to $(3.6 \pm 3.1) \times 10^{-5}$ (Na$^{131}$I) h$^{-1}$ $^2)$. Our second results (Table 3) shows an acute dependency of the dispersal rate on the wind conditions. With increasing the wind velocity, the evaporated amount of the solution increases, and the dispersal rate increases. The larger dispersal rate can be explained by the larger wind velocity in this study (0.35–0.60 m s$^{-1}$) than those of the literature (0.10–0.30 m s$^{-1}$). This result is very suggestive of that a glovebox, instead of a local ventilation system, is much more suitable for the use for $^{131}$I because it suppresses the dispersion under the condition with the less wind velocity.
3-2. α and γ spectrometry of 225Ac (dried nitrate salt)

Aliquot of the solution (about 10 μL) was sampled from the 225Ac stock solution, and diluted by 10 mL of pure water, and 10 μL was dropped onto the glass plate. After the drop was dried, α spectrum was obtained (Fig. 4). In the spectrum whose accumulation time is 1 hour, the peaks of 225Ac, and its α-active descendants (221Fr, 217At, and 213Po) were shown. This sample was only used for obtaining the spectrum, but not used for the quantitative standard.

The count rates of α and γ emissions measured for the 225Ac standard samples are shown in Fig. 5. The count rates for α emissions of the four nuclides along the decay series gave the similar values by reflecting an identical branching ratio of α decay. Contrary, the count rates for γ emissions differ depending on the emission yield of the nuclides. For the standard sample for γ spectrometry, 1 mL of the 225Ac stock solution was sampled in a PP tube.

3-3. Dispersal rate in operations with 225Ac samples

3-3-1. Trends in dispersal rates

Table 4 summarized the conditions, the measurement results, and the determined dispersal rates. The measurement results are shown in counts. The dispersal rate [h^{-1}] determined experimentally are those of filters (η_{Filter}), and those of films (η_{Film}). The upper part of the table concerns the experiments of the stirring of the various solutions of 225Ac. The lower part of
that corresponds to the various operations of 0.05 M nitric acidic solution of $^{225}$Ac.

In Table 4, both results from the short and the long measurements are shown separately. In many cases, those behaviors both in short and the long measurements coincide with each other. In such cases, the largest dispersal rate (indicated by the asterisks in the table) was selected under the same condition.

In Table 4, in some combinations of chemical operations and/or chemical status, curious behaviors are found in $^{213}$Po counts described in Italic values. In such conditions, radioactive equilibrium through the series are not attained, i.e. descendants of $^{225}$Ac are suggestive of being directly arrived at the samples. The attainment of the equilibrium is checked in each cases, and will be dealt in each discussion.

The values of $\eta_{\text{exhaust}}$ and $\eta_{\text{surface}}$ in Table 5 were calculated by applying eqs. (7) and (8) to the adopted values of $\eta_{\text{Filter}}$ and $\eta_{\text{Film}}$. As described just above, the values with asterisks in Table 4 are selected to preserve a margin for error on the safe side. At the same time, the information on the waiting time included in Table 4 is eliminated in Table 5. Finally, the total dispersal rate was obtained by the sum of them, as given by eq. (8).

It should be also mentioned that the collection efficiencies $\epsilon_{\text{collection}}$ have different values; 0.6 for nitric acid, 0.8 for phosphate buffer, and 1 for MES buffer. This tendency shows that large values for the larger pH and/or complexing condition. However, the numbers of the independent $\epsilon_{\text{collection}}$ values are only three. As can be understood in eq. (9), the determination of $\epsilon$ requires both activities for the consecutive two filters, Filter-A and Filter-B. The values were not obtained in all systems, partly because of the measurement schedule of the $\alpha$ spectrometer was almost full. Therefore, we introduced an assumption to apply the identical value to similar chemical operations/status. This assumption always increases the dispersal rate eq. (7) by factors of $1 \sim 1.7$ corresponding to the $\epsilon$ values of $1 \sim 0.6$. Therefore, an introduction of the assumption could be rationalized in terms of the margins required on the safe side.

Figure 6 shows graphical presentation of the dispersal rate of $^{225}$Ac, which is the summary of Table 5. In the determination of $\eta$ values, the largest values including the detection limit are cited in order to preserve a margin on the safe side.

3-3-2. Radioactive equilibrium through the series including volatile $^{217}$At

The activities of $^{213}$Po were detected in the filters in many of our experiments (Table 4), and the result indicates that $^{225}$Ac, or one or more of the daughter(s) dispersed and reached at the filter. One may ascribe the dispersion of $^{213}$Po to $^{225}$Ac itself from the source. Another mechanism to produce $^{213}$Po on the filter may be attributed to its volatile ancestor $^{217}$Rn, which is generated from $^{217}$At by $\beta^{-}$ decay at the yield of $7 \times 10^{-5}$. A remaining possibility might be the path through $^{217}$At–$^{213}$Bi, because Astatine is suggestive of volatility on the basis of the second lowest boiling point of 610 K in Fig. 3, where the lowest is 211 K for Radon. The absolute differences required to distinguish among the three modes of dispersion lie in the time period required for attainment of equilibrium. The path through $^{217}$Rn ($T_{1/2} = 0.54$ s) results in the equilibrium attainment in the short period (about 10 times of 4.9 min; less than 1 hour), and that through $^{217}$At–$^{213}$Bi (45.59 min) leads to the longer period up to nearly 10 hours (10 times of 45.59 min). The other path through $^{225}$Ac (9.92 d) leads to the longer period.

In an attempt to distinguish among these two paths, a combination of two measurements modes was adopted here, i.e. the short time measurements (3,600 or 5,000 s) just after the sampling, followed by the long time one (36,000 or 50,000 s). Our results indicate that in many experiments the activities of $^{213}$Po exceeded (as shown in Italic counts in the Table 4) the expected ones as in the radiochemical equilibrium of the $^{225}$Ac–$^{221}$Fr–$^{217}$At series. The general disagreement in the
The excess activities of 213Po are seen both in the short and the long measurement modes, and the results are indicative of the independent from the nature of the solutions (Table 5). The smaller-than symbol ("<") indicate the detection limit where one count is assumed. The two operations of evaporation including heating and evaporation nitric acid Filter-A (3) and films (2) respectively. The stirring operation of various solutions, the set area ratios are 7.11, 1.94 \times 10^{-2}, and 5.82 \times 10^{-3}. Stirring of various solutions (Table 4).

Table 4. Experimental dispersal rate [h^{-1}] of filters (\eta_{\text{Filter}}) and films (\eta_{\text{Film}}) determined in operational conditions.

| Samples for measurements | Operation | Time [h] 4) | Counts\(^b\) | Evaluation for 225Ac\(^7\) |
|--------------------------|-----------|-------------|--------------|----------------------------|
|                          | Filter-B 1) | 0.2 - 1 | 2 | 1 | 8 \times 10^{-9} | 0.8 |
|                          | Filter-A 1) | 0.2 - 1 | 5 | 2 | 1 | 58 | 8 \times 10^{-8} \* | 0.6 |
|                          | Film-U 2)  | 0.2 - 1 | 0 | 2 | 0 | 0 | < 2 \times 10^{-8} |
|                          | Film-M 2)  | 0.2 - 1 | 0 | 1 | 0 | 0 | < 2 \times 10^{-8} |
|                          | Film-L 2)  | 0.2 - 1 | 0 | 1 | 0 | 2 | < 2 \times 10^{-8} |
| phosphate buffer         | Filter-B 1) | 3.3 - 13.9 | 2 | 5 | 1 | 1 | 8 \times 10^{-9} | 0.8 |
|                          | Filter-A 1) | 0.5 - 1.39 | 3 | 4 | 2 | 29 | 1 \times 10^{-7} \* | 0.8 |
|                          | Film-U 2)  | 92.7 - 1.38 | 0 | 0 | 0 | 0 | < 5 \times 10^{-8} |
|                          | Film-M 2)  | 70.4 - 1.39 | 1 | 1 | 0 | 0 | 5 \times 10^{-8} \* |
|                          | Film-L 2)  | 67.8 - 1.39 | 0 | 0 | 0 | 1 | < 5 \times 10^{-8} |
| MES buffer with DOTA     | Filter-B 1) | 0 - 1 | 0 | 0 | 0 | 1 | < 8 \times 10^{-8} | 1 |
|                          | Filter-A 1) | 1.2 - 10 | 3 | 5 | 4 | 15 | 1 \times 10^{-7} \* | 1 |
|                          | Film-U 2)  | 0.1 - 1 | 1 | 0 | 0 | 0 | 7 |
|                          | Film-M 2)  | 1.3 - 10 | 5 | 8 | 5 | 3 | 3 |
|                          | Film-L 2)  | 0.1 - 1 | 1 | 2 | 1 | 8 | 7 | 4 \times 10^{-7} \* |
|                          | Filter-B 1) | 1.3 - 10 | 5 | 3 | 3 | 20 | 3 | 2 \times 10^{-7} \* |
|                          | Filter-A 1) | 0.2 - 1 | 8 | 15 | 2 | 173 | 1 \times 10^{-7} \* | 0.6 |
|                          | Film-L 3)  | 0.2 - 10 | 14 | 10 | 4 | 21 | 3.58 \times 10^{-7} \* | 0.6 |
|                          | Filter-A 1) | 13.7 - 10 | 17 | 16 | 16 | 13 | 5.8 \times 10^{-8} \* | 0.6 |
|                          | Film-L 3)  | 0.3 - 1 | 6 | 9 | 3 | 4 | 1 \times 10^{-7} \* |
|                          | Filter-B 1) | 3.1 - 10 | 70 | 45 | 42 | 28 | 2.3 \times 10^{-7} \* |
|                          | Filter-A 1) | 0.2 - 10 | 44 | 98 | 6 | 927 | 8.3 \times 10^{-8} \* | 0.6 |
|                          | Film-L 3)  | 0.3 - 10 | 12 | 8 | 4 | 4 | 2.4 \times 10^{-8} \* |

Offset area ratios are 7.11, 1.94 \times 10^{-8}, and 5.82 \times 10^{-9}, for 1) to 3), respectively.

4) The values shows waiting time and the measurement time, respectively.
5) Corrected to the time when \(\alpha\) spectroscopy of the standard solution of 225Ac was measured.
6) The smaller-than symbol ("\(<\)"") indicate the detection limit where one count is assumed.
7) Asterisk indicates the value is adopted because it is the largest among the same condition.
8) Italic value for \(\epsilon\) indicates it is determined in the same condition.
9) Italic value for 213Po counts indicates it is out of equilibrium in the decay.

activities of the 217At–213Po pair excludes the 217At–213Bi path. The excess activities of 213Po are seen both in the short and the long measurement modes, and the results are indicative of the dispersion of 217Rn, but not 225Ac. However, it should be mentioned that another part of the experiments without Italic values shows no evidence of deviation from the equilibrium starting from 225Ac.

3-3-3. Stirring of various solutions

For the stirring operation of various solutions, the magnitude of \(\eta_{\text{surface}}\) is one order larger than that of \(\eta_{\text{exhaust}}\), independent from the nature of the solutions (Table 5). The excess surface contamination (\(\eta_{\text{surface}}/\eta_{\text{exhaust}} \sim 10\)) suggests a dispersion mode under a constant air current. A dependence of the total dispersal rate on the basicity (pH) of the solution was found, as is the smallest for 0.05 M nitric acidic solution (< 2 \times 10^{-6} h^{-1}), and the largest for DOTA complex in MES buffer (3 \times 10^{-5} h^{-1}). The tendency indicates that the neutral condition required to label the complex with the radioactive 225Ac enhances the dispersal rate.

3-3-4. Evaporation and dripping

The two operations of evaporation including heating and dripping shows very contrasting behavior in dispersion of 225Ac.
Under the evaporation operation, the surface contamination is not dominant ($h_{\text{surface}}/h_{\text{exhaust}} \sim 3.9$). The dispersion under the evaporation condition may progress through the steam with small liquid particles. Contrary, the dripping shows large dispersion ($h_{\text{surface}}/h_{\text{exhaust}} \sim 1.89 \times 10^{-5}$), whereas the dispersion in exhaust is as small as that for stirring of 0.05 M nitric acidic solution. The remarkably large dispersion on surface ($h_{\text{surface}}/h_{\text{exhaust}} \sim 200$) is the result of the splash of the droplets.
Table 6. Difference of activities $n$ [cps] of $^{225}$Ac and its descendant nuclides in samples\(^{11}\). Activities\(^{2}\) in $\gamma$ measurements before ($A_0$) and after centrifuge ($A_1$) and vortex mixing ($A_2$) procedures.

| Operation            | $^{225}$Ac (150 keV) | $^{221}$Fr (218 keV) | $^{213}$Bi (440 keV) |
|----------------------|----------------------|----------------------|----------------------|
|                      | sample               | bag                  | sample               | bag                  | sample               | bag                  |
| centrifuge           | $A_1 - A_0$          | $-0.033 \pm 0.033$   | $< 0.02$             | $-0.027 \pm 0.049$   | $< 0.05$             | $-0.013 \pm 0.049$   | $< 0.01$             |
| vortex               | $A_2 - A_0$          | $0.003 \pm 0.033$    | $< 0.02$             | $-0.067 \pm 0.049$   | $< 0.03$             | $0.030 \pm 0.049$    | $< 0.01$             |

1) The average and the standard deviation of repeated experiments for three times.  
2) The smaller-than symbol ("<") indicate the detection limit where one count is assumed.

In addition, it is worthwhile to note that a very large activities of $^{213}$Po were found in the evaporation. This could be explained by gaseous $^{213}$Rn.

3-3-5. Standing of dry salt

The dispersion rate $\eta$, and the ratio $\eta_{\text{surface}}/\eta_{\text{exhaust}}$ for the dry salt are similar to those under the stirring operation of 0.05 M nitric acidic solution (Table 5). The handling of the unsealed solid salt of $^{225}$Ac nitrate results in a moderate dispersion of $^{225}$Ac ($\eta = 2.1 \times 10^{-6}$ h\(^{-1}\)). However, the largest activity of $^{213}$Po throughout this study was found (Table 4), which can be attributed to the dispersion of its ancestor $^{213}$Rn.

3-3-6. Comparison with operational factors

The dependence of the total dispersal rate $\eta$ on the operations yielded two classes of operations with low values ($2 \sim 4) \times 10^{-6}$ h\(^{-1}\) and high values ($2 \sim 4) \times 10^{-5}$ h\(^{-1}\). The operations with the low $\eta$ includes the stirring, heating and evaporation of nitric acidic solution, and standing of nitrate salt. The operations with the high $\eta$ includes dripping of nitric acidic solution, and DOTA complex in MES buffer.

This trend in dispersal rates agrees with the idea appeared as the operational factors for laboratory use of radioactive materials as described in the ICRP Publication 5\(^{4}\). The operations with the low $\eta = (2 \sim 4) \times 10^{-6}$ h\(^{-1}\) is not the “very simple” wet operation exemplified as treating only aliquots of solutions, but could correspond to the “normal wet operations” (operational factor = 1). The operations with the high $\eta = (2 \sim 4) \times 10^{-5}$ h\(^{-1}\) is corresponding to the “complex wet operations” (operational factor = 0.1).

3-4. Surface contamination in centrifuge and vortex mixing

The contaminations to circumstances by the centrifuge, and by the voltex mixing were evaluated by the activities of the bags which were used to surround the PP tube before ($A_0$), and those after the centrifuge ($A_1$) and the vortex mixing ($A_2$), as summarized in Table 6. The experiment is composed of independent three samples, and the differences ($A_1-A_0$ and $A_2-A_0$) are shown with the average values and the standard deviations. The result shows that no activity was found within measurement error. The centrifuge and the vortex mixing are found to have no dispersion, if the container has a strict sealing.

3-5. Concentrations of radionuclides in waste water

The $\gamma$ activities of the rinse solutions and the rinsed tools were measured and summarized in Table 7. Even the radioactivity of the first rinse is about three orders of magnitude ($< 8.6 \sim 1.9) \times 10^{-3}$ smaller than that of the sample solution which had been contained in the beaker. If the washing is repeated twice and the rinses are recovered, the concentration in the third rinse solution, i.e. the waste water, can be managed at the level of five orders of magnitude ($< 5 \sim < 4) \times 10^{-5}$ smaller than that of the first one. Conclusively, the concentration in the waste water is found to be suppressed to the activity five-orders smaller than that of the sample, if the first and the second rinses are recovered.

4. Conclusions

Actinium-225 is one of the most promising nuclides for nuclear medicines. Since the dispersions of $^{225}$Ac during chemical experiments had not been determined, dispersal rate of 0.01 has been uniformly set in safety side instead. This large margin, in turn, will impose the facilities for administration, for manufacturing, and for R&D of nuclear medicines too large costs for radioactive protections. This study was conducted to determine the experimental dispersal rate, surface contamination, and waste water of $^{225}$Ac.

The total dispersal rate $\eta$ can be classified into two classes operations with low values ($2 \sim 4) \times 10^{-6}$ h\(^{-1}\) and high values
(2 ~ 4) \times 10^{-5} \, h^{-1}. In all cases the dispersal rates of the surface contamination ($\eta_{\text{surface}}$) exceeds those of the exhaust ($\eta_{\text{exhaust}}$) by a factor of 10 or larger ($\eta_{\text{surface}}/\eta_{\text{exhaust}} > 10$). In terms of the nature of the liquid, the nitric acidic solution gives the lowest $\eta_{\text{exhaust}}$ value, and the solution with DOTA complex gave the value more than one order of magnitudes larger. Concerning the types of the operations, dipping gave small $\eta_{\text{exhaust}}$ Value, but $\eta_{\text{surface}}$ value which was more than two orders of magnitudes larger than $\eta_{\text{exhaust}}$. Also, the second largest $\eta_{\text{exhaust}}$ values was obtained during the heating and the evaporation.

Our result clearly shows the comparison of $\eta$ values between $^{225}$Ac and $^{131}$I. Under the operational condition of acidic solutions and the wind velocity of 0.35 m s$^{-1}$, the dispersal rate of $^{225}$Ac is $2 \times 10^{-6} \, h^{-1}$, which is more than a magnitude smaller than $^{131}$I ($7.4 \times 10^{-5} \, h^{-1}$). It means that the use of the glovebox is not essential for $^{225}$Ac, and the necessity of the equipment, i.e. gloveboxes or local ventilation systems, can be discussed on the basis of the dispersal rate determined in this study.

Our experiments agrees with the modifying factors of ca. 0.1 when applied to “complex” chemical reactions in agreement with the ICRP Publications 5$^6$. The values of the transfer from the $^{225}$Ac obtained in this study can be used to evaluate the transfer in one day (8 hours/day). The transfer is more than two orders of magnitude smaller than the specific value of 0.01 in the present regulation.

**Acknowledgements**

We would like to thank Yoshihide Nakamura, Japan Radioisotope Association for his helpful discussions throughout the investigation. This study was funded by the Radiation Safety Regulation Research Strategic Promotion Project from the Nuclear Regulation Authority, Japan.

**References**

1) C. Kratochwil, F. Bruchertseifer, F. L. Giesel, M. Weis, F. A. Verburg, F. Mottaghy, K. Kopka, C. Apostolidis, U. Haberkorn, and A. Morgenstern. $^{225}$Ac-PSMA-617 for PSMA targeting alpharadiation therapy of patients with metastatic castration-resistant prostate cancer. *J. Nucl. Med.*, 57:1941–1944, 2016.

2) T. Muto, S. Takada, N. Ito, A. Kitahara, H. Chisaka, and M. Ikeda. Determination of radioactivities released from radioactive materials—a comparison of dispersal rates for various nuclides in the solution under normal chemical operations—. *RADIOISOTOPES*, 31:641–647, 1982.

3) S. Takada, T. Muto, N. Ito, A. Kitahra, H. Chisaka, I. Kuze, T. Tateishi, Y. Nakamura, and M. Ikeda. An estimation for the dispersal rates of radioactive materials under various handling. *RADIOISOTOPES*, 32:260–269, 1983.

4) International Commission on Radiological Protection. Handling and disposal of radioactive materials in hospitals and medical research establishments. Technical report, ICRP Publication, 1964.

5) International Commission on Radiological Protection. The handling, storage, use and disposal of unsealed radionuclides in hospitals and medical research establishments. Technical report, ICRP Publication, 1977.

6) L. Dominguez-Gadea and L. Cerezo. Decontamination of radioisotopes. *Reports Practical Oncology Radiotherapy*, 16:147–152, 2011.

7) OECD/NEA. *Radioactivity Measurements at Regulatory Release Levels*, 2006.

---

**Table 7.** Dependence of activities $n$ found in rinse and tools on the number of times of rinse. The beaker was once partly filled with $^{225}$Ac nitric acid solution (the sample). The ratio of activities to standard used to convert to activities.

| Samples          | $^{225}$Ac [cps] | $^{221}$Fr [cps] | $^{213}$Bi [cps] | Ratio of counts to the sample |
|------------------|------------------|------------------|------------------|------------------------------|
| Rinse No.1       | 0.14±0.03        | 2.32±0.06        | 2.73±0.06        | <8.6×10$^{-3}$               |
| Rinse No.2       | <0.06            | 0.30±0.03        | 0.35±0.02        | <4×10$^{-3}$                 |
| Rinse No.3       | <0.04            | <0.05            | <0.06            | <5×10$^{-5}$                 |
| Rinse No.4       | <0.03            | <0.06            | <0.02            | <4×10$^{-5}$                 |
| Rinse No.5       | <0.04            | <0.07            | <0.05            |                              |
| Rinse No.6       | 0.05             | 0.04             | 0.02             |                              |
| Rinsed beaker    | <0.03            | 0.09±0.03        | 0.14±0.02        |                              |
| Rinsed tips      | <0.03            | <0.04            | <0.04            |                              |
| Rinsed stirrer tips | <0.03       | <0.08            | <0.05            |                              |

1) The smaller-than symbol (\(<\)) indicate the detection limit where one count is assumed.
8) The International Commission on Radiological Protection. 1990 recommendations of the international commission on radiological protection. Technical report, ICRP Publication, 1991.

9) Japanese Society of Radiological Technology and Japanese Society of Nuclear Medicine Technology. Guideline for management of radioisotope concentrations in exhaust gas and waste water. *Japanese J. Radiological Technology*, 57:264–301, 2001.

10) C. Apostolidis, R. Molinet, G. Rasmussen, and A. Morgenstern. Production of Ac-225 from Th-229 for targeted $\alpha$ therapy. *Anal. Chem.*, 77:6288–6291, 2005.

11) B. Zielinska, C. Apostolidis, F. Bruchertseifer, and A. Morgenstern. An improved method for the production of Ac-225/Bi-213 from Th-229 for targeted alpha therapy. *Solvent Extraction and Ion Exchange*, 25:339–349, 2007.

12) K. A. Deal, I. A. Davis, S. Mirzadeh, S. J. Kennel, and M. W. Brechbiel. Improved in vivo stability of actinium-225 macrocyclic complexes. *J. Med. Chem.*, 42:2988–2992, 1999.

13) International Atomic Energy Agency. Live chart of nuclides. https://www-nds.iaea.org/, 2019.