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Accumulation of Tritium and Other Undesirable β-Emitting Radionuclides in the Production of Radiopharmaceuticals for PET Diagnostics

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Abstract—The article deals with the problem of formation of undesirable β-emitting radionuclides (RNs) in the production of radiopharmaceuticals for PET diagnostics. It is found that tritium is the main trace RN formed by the reaction $^{18}O(p,t)^{16}O$ during irradiation of water $[^{18}O]H_2O$ with protons. Other trace β emitters in water accumulate mainly as a result of leaching of activated target wall materials. The possibility of using the activity of tritium in water $[^{18}O]H_2O$ as an indicator of its re-enrichment is shown. The necessity of controlling the content of trace β-emitting RNs in intermediate products, production waste, and final radiopharmaceuticals is demonstrated.

Keywords: radiopharmaceuticals, cyclotron, $[^{18}O]H_2O$, tritium, β-emitting radionuclides
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INTRODUCTION

Positron emission tomography (PET) is a dynamically developing method for early diagnosis of cancer as well as neurological and cardiac diseases that utilizes intravenous administration of radiopharmaceuticals (RP) based on short-lived positron-emitting radionuclides with half-life $t_{1/2}$ = 10–120 min [1]. PET examinations account for the major share of ~40 million nuclear medicine diagnostic procedures performed annually worldwide. At the same time, the demand for positron-emitting radioisotopes is increasing by 5% annually worldwide.

The most common radionuclide for PET diagnostics is ^{18}F, which is obtained by irradiation of water ($H_2{}^{18}O$) enriched in ^{18}O up to 95–97% by protons with energy of 9–20 MeV. The target nuclide is accumulated as a result of the (p,n) reaction. The reaction $^{18}O(p,t)^{16}O$ with a threshold energy of 3.91 MeV [2], the product of which is tritium, occurs at the same time. ^3H is also formed by the interaction of protons with atoms of the entrance window (Fe, Co, Ni) and the target body, but the cross sections of these reactions are small ($\leq 10^{-3}$ b); therefore, the probability of tritium entering the irradiated $H_2{}^{18}O$ as a result of such a process is low.

Tritium is a pure β emitter with $E_{\beta\,\max}$ = 18.58 keV and a half-life of 12.5 years. It decays according to the scheme $^3H \rightarrow {}^3He^+ + e^-$. The electrons emitted during this decay have a range of ~6 mm in air and ~5 μm in water. Tritium cannot be detected by most dosimeters because no γ radiation is observed during its decay.

Tritium beta radiation is completely trapped by the skin and can only pose a hazard to personnel if ingested. Entering the body in the form of tritium water ^3H_2O or tritium organic compounds, ^3H can replace hydrogen atoms in biologically active molecules, which can lead to radiation damage of cells during tritium decay.

Tritium contamination of equipment is a serious problem in radiochemical facilities. Tritium easily diffuses in almost all structural materials (metals, polymers, and glasses) and dissolves in them. Decontamination of units and containers in contact with tritium by immersion in pickling and standard desorbing solutions does not give satisfactory results. As a result of radioactive decay of tritium, helium is formed, which with time accumulates in the volume of structural

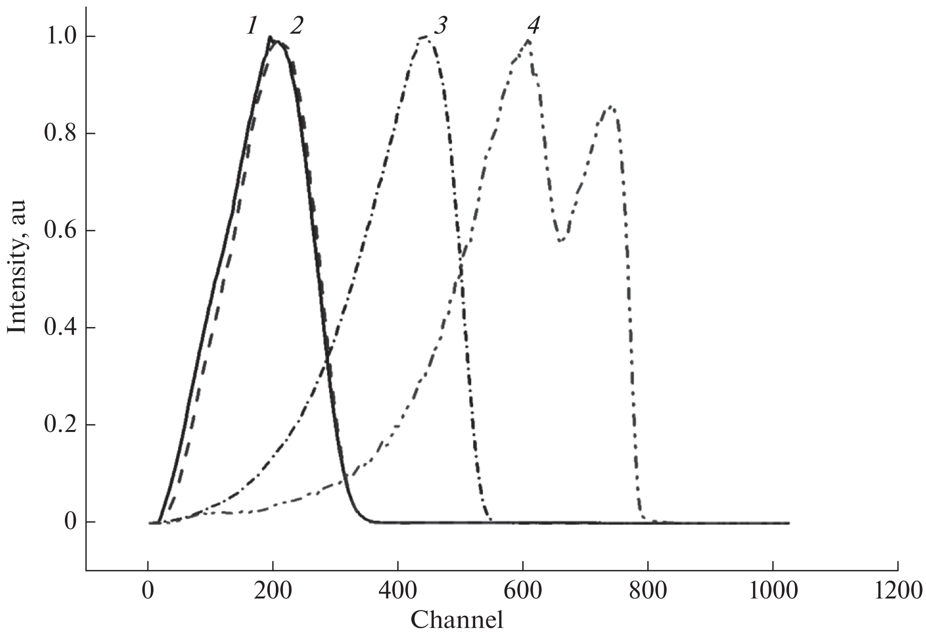

Fig. 1. β spectrum of $[^{18}O]H_2O$ water irradiated at the Cyclone 18/9 HC measured by liquid scintillation spectroscopy: (*1*) analyzed sample (solid line); (*2*) ^{3}H reference (dashed line); (*3*) ^{14}C reference; (*4*) ^{90}Sr + ^{90}Y reference.

materials and leads to degradation of their physical and chemical properties (so-called *aging*).

The majority of γ-emitting radionuclides (RNs) detected during the production of RPs for PET are also β emitters [3], and their emission energy varies widely, up to ~900 keV. The mentioned circumstances make it necessary to control the content of β-emitting RNs in intermediate products, production wastes, and final radiopharmaceuticals. In addition, it is necessary to monitor the working premises of the PET center in order to assess the doses received by both staff and patients [2]. The aim of the present work is to investigate the accumulation of unwanted β-emitting RNs during the production of different ^{18}F-based RPs.

MEASUREMENT METHODOLOGY

The γ-emitting radionuclides were identified and their activity was determined using a spectrometer on especially pure germanium: GEM40-83/DSPEC jr 2.0 detector system; energy range of 14.5–2911.4 keV; resolution of 0.182 keV/channel. The radionuclides were identified by correlating the γ-quantum energies determined experimentally with reference values. Owing to high activity, measurements were carried out at least two days after the last irradiation.

The content of β-emitting radionuclides was monitored using a HIDEX 300 SL automatic liquid scintillation spectrometer with TDCR counting and MKS-AT1315 gamma-beta spectrometer. For the HIDEX 300 SL, the energy range was 0–2 MeV for β particles, the interval was 0.182 keV/channel, and the efficiency was over 70% for tritium and over 95% for ^{14}C. The average background for β particles was 9 pulse/min. A toluene-based liquid scintillator was used. Samples of 1 mL were diluted in 19 mL of liquid scintillator. The measurement time of the β spectrum was 1000 s. For the MKS-AT1315, the beta energy range was 0.15–3.5 MeV. The average background for β particles was 270 pulse/min and the sensitivity for ^{90}Sr in 0.03L geometry was 3.5×10^{-3} pulse L/(s Bq).

EXPERIMENTAL RESULTS

Upon irradiation of a new (“clean”) target, a single peak due to tritium emission was observed in the β spectra of irradiated $[^{18}O]H_2O$ after storage for 3 months (Fig. 1). For comparison, the spectra of calibration solutions (^{3}H, ^{14}C, ^{90}Sr + ^{90}Y) are also shown in Fig. 1.

The tritium content in irradiated water is directly proportional to the duration of irradiation and the magnitude of ionic current. The ratio of tritium and ^{18}F activities in the irradiated $H_2\,^{18}O$ water A_{H3}/A_{F18} does not depend on the current on the target and is determined mainly by the proton energy and varies from $A_{H3}/A_{F18} = 2.6 \times 10^{-6}$ at a proton energy of 9.6 MeV [2] to $A_{H3}/A_{F18} = 1.0 \times 10^{-6}$ at 16.5 MeV [4]. Monte Carlo modeling of the process gives values of tritium activity 40% higher than those obtained experimentally. According to [4], this effect is due to the deposition of the radionuclide on the target walls and polymer capillaries of the transfer line of irradiated water from the cyclotron to the fusion module. At irradiation durations exceeding the half-life of ^{18}F($t_{1/2}$ = 110 min), the A_{H3}/A_{F18} ratio slightly increases, which is due to the decay of part of the produced ^{18}F. Thus, according to our experimental data, at irradiation duration of ≥110 min and proton energy of 16.5 MeV, the A_{H3}/A_{F18} ratio increases to ~2.2 × 10^{-6}.

According to the estimates of the management of Taiyo Nippon Sanso Corporation (Japan), the world's largest producer of $^{18}O_2$ by cryogenic distillation, about half of the world's consumption of [^{18}O]H_2O is reused (or reusable) water [5]. It should be noted that when purified reclaimed water [^{18}O]H_2O is reused for RP production, there is no linear dependence of tritium activity on the irradiation dose; there is a large scatter of ^{3}H activities at close values of irradiation dose (Table 1). This is due to the fact that, as a result of enrichment of water in oxygen isotope ^{18}O by both centrifuge and distillation methods, the activity of ^{3}H will increase simultaneously with the accumulation of heavy oxygen isotopes (^{18}O and ^{17}O). In this case, most small producers often do not conduct purification from tritium after re-enrichment by oxidizing water to molecular oxygen [^{18}O]O_2 followed by its reduction with hydrogen of natural isotopic composition.

At the same time, as noted above, tritium accumulates in irradiated [^{18}O]H_2O in quite significant amounts. Thus, under routine production conditions, the tritium content in regenerated water that passed through an anion-exchange cartridge and was collected for reuse varies from 30 to 230 kBq/mL depending on the conditions of irradiation: proton beam energy, ion current value, irradiation duration, etc. [2, 6–10]. Under routine production conditions at the Cyclone 18/9 NS cyclotron with an energy of 18 MeV at an ion current of 70–80 μA and irradiation duration of 80–140 min, the specific activity of ^{3}H in regenerated water collected from 200 syntheses was 130–200 kBq/mL [5]. In comparison, the tritium content of commercially available $H_2{}^{18}O$ water varies in the range of 2.2 × 10^{-3}–0.4 Bq/mL according to different data [2, 6, 7].

The activity of ^{3}H is such that, according to the requirements of SanPIN of the Republic of Belarus no. 142 Requirements for Ensuring Radiation Safety of Personnel and Population when Handling Radioactive Waste and Hygienic Standard Criteria for Assessment of Radiation Exposure, the regenerated water containing tritium should be considered as low-level radioactive waste. Moreover, the specific activity of regenerated water from routine production is 2–3 orders of magnitude higher than the level of release from under control according to the above normative documents. There are similar requirements in the regulatory documents of the Russian Federation (OSPORB-99/2010). Taking into account the half-life of tritium ($t_{1/2}$ = 12.5 years), the problem of storage (or utilization) of regenerated water arises.

Table 1. Tritium content in regenerated [^{18}O]H_2O from different batches

Batch number	Irradiation dose, μA min	^{3}H activity, Bq	Activity/dose ratio, Bq/(μA min)
1	4700	88016	18.73
2	9867	158834	16.10
3	4884	100993	20.68
4	533	9266	17.39

Tritium, apart from the irradiated $H_2{}^{18}O$ water, was also detected in the water that passed through the anion-exchange cartridge (the so-called regenerate), in the waste of organic solvents from washing of modules (acetonitrile solution), and also in the water with which the target was washed. The main fraction of ^{3}H (about 95%) remains in the regenerate. The residue (5%) is washed off the ion exchange resin with acetonitrile, two-thirds of which (3.2%) ends up in the waste [2]. The tritium content in the 2-fluorodeoxyglucose (FDG) production waste according to [2] is 1.46 Bq/mL, which is consistent with our data. The amount of 1.6% of the generated tritium activity is carried away from the synthesis zone with gases and water vapor generated during synthesis. This amounts to about 4 × 10^{-8} of the ^{18}F activity produced in the cyclotron. Usually, in a single production cycle, the ^{18}F production rate is between 150 and 300 GBq. Accordingly, 6–15 kBq of tritium should be expected to be volatilized per one gaseous synthesis. In routine production, ~250–500 syntheses are performed during a year in single-shift operation and, accordingly, ~3–6 MBq ^{3}H are emitted with gaseous waste. Incidentally, some production sites in Russia have over 1800 syntheses of fluorine-18 per year. In choline synthesis, the volume of gaseous emissions can increase twofold but will not be higher than 3–4% of tritium activity, which is equivalent to ~1 × 10^{-7} of the ^{18}F activity produced at the cyclotron.

An assessment of tritium releases to the environment during the production of the radiopharmaceutical FDG and determination of the dose received by the population was performed in [10]. Gaseous emissions from hot laboratories were passed through charcoal filters before reaching the atmosphere. The ^{3}H content was determined by the electrolytic enrichment method with subsequent measurements on a liquid scintillation spectrometer. The average activity of tritium in the air was found to increase after the cyclotron commissioning (3 years of activity accumulation) by 3–4 times, from ~0.30 Bq/L to 0.80–1.02 Bq/L. The additional dose accumulated by the population on account of this was estimated as 0.08 mSv/year.

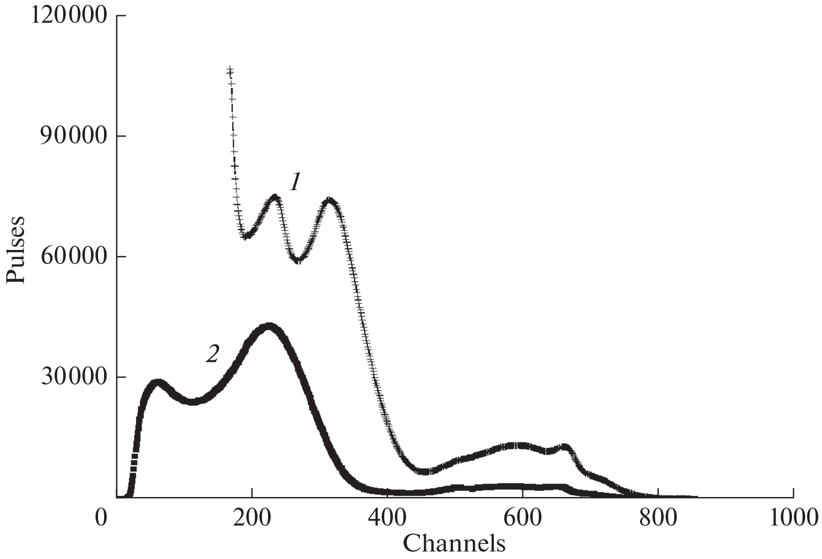

Fig. 2. β spectra of regenerated [^{18}O]H_2O after irradiation at the Cyclone 18/9 HC of target with an accumulated dose of 4000 μA h measured (*1*) 2 days and (*2*) 3 months after synthesis.

According to the data from [2, 6, 8, 11], in the finished form of most RPs (FDG, choline, and methionine), the concentration of tritium is close to the resolution limit of the measurement technique. Thus, the maximum tritium content in FDG according to [9] was 0.269 ± 0.016 Bq/mL, which is almost five orders of magnitude lower than the tritium content in irradiated water. Among the RNs, the exception is Na^{18}F. The ^{3}H content in the RP ^{18}F-NaF was about three orders of magnitude higher than in FDG and amounted to 560 Bq/mL, which is due to the features of its production technology.

Tritium accumulates in the walls of the cyclotron target and transfer line owing to diffusion from irradiated water. The target body material Nb easily absorbs hydrogen with the formation of a solid solution of hydrogen and NbH hydride, which is a gray crystalline powder. Gray deposition on the surface of niobium targets was visually observed by us and the authors of [12] after prolonged irradiation (more than 2000 μA h). As is known, the entrance window of the cyclotron water target is made of Havar alloy, the main components of which are Fe, Ni, and Co [3]. Tritium accumulation can lead to premature deformation or even rupture of the entrance window of the target. Therefore, it is advisable to periodically wash the target to remove the residues of irradiated water enriched with tritium. It should be noted that, after washing the target, the tritium content in the water varies greatly according to the data of different researchers. Thus, according to [13], the specific activity of ^{3}H in the wash water is 1.4 Bq/mL, while the authors of [8] give a significantly higher value of 92 Bq/mL. The reason for this discrepancy is not quite clear, but it may be due to different target design, volume (1.3 and 2.4 mL), target material (Nb and Ti), target purging mode, volume of wash water, and number of production cycles before target purging.

In the case of irradiation of targets with large accumulated doses (over 2500 μA h), the β spectra of regenerated water [^{18}O]H_2O are significantly transformed (Fig. 2) They differ cardinally from the similar spectrum after irradiation of a “clean” (unirradiated) target (Figs. 1 and 2). In addition to the maximum due to tritium, the spectra show a number of other maxima in both the low- and high-energy parts of the spectrum. Moreover, storage for 3 months leads to a significant transformation of the spectra, the intensity of the low-energy wing of the spectrum of regenerated water sharply decreases, and the maximum in the region of channel 300 disappears, while the intensity of the high-energy wing (from channels 450 to 700) decreases not so dramatically. As a result, the peak in the region of channel 200 due to tritium becomes dominant.

Experimental results indicate the presence in regenerated [^{18}O]H_2O of a number of β-emitting nuclides with different energies of emitted electrons and half-lives. Their total activity in the first few days after synthesis is much higher than that of ^{3}H. Strong radiation in the low-energy region of the β spectra when irradiating a “dirty” target increases the error in measuring the tritium concentration. The shape of its band is strongly distorted (Fig. 2, curve *1*). The ^{3}H content in irradiated water can be estimated quite reliably by scintillation spectrometry only after long (about 3 months) storage, when the tritium band becomes dominant in the β spectrum (Fig. 2, curve *2*).

It should be noted that after irradiation of the dirty target (with an accumulated dose of ~7000 μA h), the content of tritium and other β-emitting radionuclides in the prepared radiopharmaceuticals ([^{18}F]methylcholine and [^{18}F]FDG) was below the detection limit of the used technique [14]. This is due to the high degree of purification of the above preparations from unwanted radionuclides during synthesis.

In order to analyze the obtained experimental data, the authors used previously published materials [3] on the study of γ-emitting radionuclides during irradiation of targets with a large accumulated dose. In [3], more than 20 undesirable γ-emitting RNs forming ^{18}F-based RPs during fabrication were identified. Most of them are β emitters: they mostly decay via K-capture or emit positrons (β^+ decay), less frequently electrons (β^- decay).

The dominant radionuclides in the γ spectra of regenerated water measured on the third day after synthesis are cobalt isotopes ^{56}Co and ^{58}Co with half-lives of 77.3 and 70.9 days, respectively, and activity of ~(5–10) × 10^4 Bq/mL each at the end of the pharmaceutical synthesis [3]. They have a number of lines of β emission in the range of 195–1500 keV and can determine the appearance of the high-energy region of β spectra (around channels 500–700) of regenerated water.

The signal in the low-energy region of the β-radiation spectrum is most likely due to Auger electrons as well as the knockout of low-energy electrons by γ quanta and X-rays when passing through water [5]. Auger electrons and X-rays are produced by the decay of radionuclides in the K-capture process. In [3], radioisotopes Re, Tc, Ni, and Mn with specific activity in the range of 50–1000 Bq/mL at the end of synthesis were observed in γ spectra, which are short-lived (half-life less than a week) and decay by K-capture accompanied by X-ray emission. Most likely, these radionuclides are responsible for the low-energy part of the β spectra of the regenerated water.

One should also take into account the possibility of formation of the isotope ^{55}Fe during irradiation, which is formed during decay of short-lived ^{55}Co [3]. It is also formed when Havar foil is irradiated with protons by the reaction ^{55}Mn(p,n)^{55}Fe with a threshold energy of 1.032 MeV. The above RN emits in the X-ray range (energy of 5.9 keV), and for this reason, it was not detected by us when measuring γ spectra. ^{55}Fe was observed in [15] when irradiating an aqueous target with the entrance window of their Havar foil at the 9.6 MeV CYPRIS MINI trace cyclotron. Its specific activity in the regenerated water can be quite high. For example, according to [15], it was the maximum of all detected RNs and amounted to 1243 Bq/mL on the third day after synthesis. The radioisotope ^{55}Fe decays by K-capture and is a long-lived radionuclide with a half-life of 2.7 years. It is probably responsible for the low-energy peak in the region of channel 20 remaining after a 3-month exposure.

In [15], another low-energy radionuclide was found in the irradiated water [^{18}O]H$_2$O, ^{59}Ni with the energy of 6.9 keV and half-life $t_{1/2} = 7.5 \times 10^4$ years. This RN should form in the Havar foil by the reaction ^{59}Co(p,n)^{59}Ni. Its specific activity in the regenerated water was three times lower than that of ^{55}Fe. It should also contribute to the low-energy peak in the channel 20 region after a 3-month exposure.

CONCLUSIONS

The article considered the problem of the formation of β-emitting nuclides in the production of radiopharmaceuticals for PET diagnostics. The studies showed that tritium is the main trace radionuclide formed by the ^{18}O(p,t)^{16}O reaction when water is irradiated with [^{18}O]H$_2$O protons. Other β emitters in water accumulate mainly as a result of leaching of activated materials of the target wall. The possibility of using measurements of tritium activity in water [^{18}O]H$_2$O as an indicator of its re-enrichment was demonstrated. The necessity of controlling the content of β-emitting RNs in intermediate products, wastes of production, and final radiopharmaceuticals as well as of monitoring the working premises of the PET center to reduce dose loads on the personnel and environmental pollution was shown.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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