UPDATE ON CYCLOTRON PRODUCTION STUDIES OF NO-CARRIER-ADDED: COPPER-64, ASTATINE-211/POLONIUM-211G, RHENIUM-186G

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Abstract

Selected results are presented and discussed concerning nuclear data relevant to the production of innovative medical radionuclides (RNs) of special interest, measurements of excitation functions of the involved nuclear reactions, in comparison with the corresponding theoretical calculations. Moreover, at the Radiochemistry Laboratory of Accelerators and Applied Superconductivity Laboratory, LASA, several *high specific activity* radionuclides in *no-carrier-added* form (NCA) have been radiochemically processed by selective methods and submitted to quality control/assurance tests, for both fundamental research and medical applications.

INTRODUCTION

A series of *high specific activity* (A_S) accelerator-produced radionuclides in *no-carrier-added* (NCA) form, for uses in metabolic radiotherapy applications and in related PET and SPET radiodiagnostics as well have been critically investigated and/or fully revisited, with accurate and precise thin- and thick-target yield measurements:

1. NCA ^{211}At/^{211g}Po, cyclotron produced by ^{209}Bi(α,2n) reaction, with *internal spike* of the γ emitter ^{210}At from ^{209}Bi(α,3n) reaction (*i.e.* and a small amount of ^{210}Po as radiotoxic long-lived impurity by-product), for high-LET metabolic radio- and immuno-radiotherapy.
2. NCA ^{64}Cu, produced by ^{nat}Zn(d,αxn), ^{nat}Zn(d,2pxn) and ^{64}Zn(d,2p) reactions for simultaneous β^+/β^- metabolic radiotherapy with simultaneous PET imaging capability, including the short-lived radionuclidic impurity ^{61}Cu, and also ^{66,67}Ga as relevant co-produced radionuclides.
3. NCA ^{186g}Re, produced by ^{nat}W(p,n) and ^{186}W(p,n) reactions, for bone metastases pain palliation by β^- (1.1 MeV End Point) metabolic radiotherapy and simultaneous SPET imaging. Specific receptor binding studies with [^{186g}Re]-labelled oligopeptides are envisaged too .

The nuclear data relevant to the excitation functions of the involved nuclear reactions, including the ones concerning the production of radionuclidic impurities, are discussed through appropriate comparison (IAEA Coordinated Res. Projects) of present and other available and critically selected experimental values previously published and with model calculations presently done.

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EXPERIMENTAL

All targets have been irradiated at the Scanditronix MC40 cyclotron (*K=38*) of JRC-Ispra, that delivers some tens μA variable energy p or α beams with energies up to 38 MeV and d beams with energies up to 19 MeV [1-14].

Concerning the At radionuclides, ^{211}At (at equilibrium with the ultra-short-lived ^{211g}Po) is the most promising for labelling drugs and radiopharmaceutical compounds for high-LET metabolic radionuclide therapy (HLRNT). A good choice for a production method of ^{211}At needs minimizing radionuclidic contamination by ^{210}Po radionuclides to negligible levels. The direct production method based on the nuclear reactions ^{209}Bi(α,2n)^{211}At is the most adequate, because it can be performed in a medium energy compact cyclotron, leading to high yield and low contamination by the only radioisotopic impurity ^{210}At, that can be either useful as internal γ spike, or not produced if the α beam energy is kept less than 28.61 MeV. The irradiation experiments for ^{211}At have been carried out at low beam current of alpha particles (50 to 250 nA), with an integrated beam charge of 100 and 450 μC, measured with an error smaller than 1-2% through a Faraday cup connected to a charge integrator. Besides, the reliability of beam charge integrator was checked by thin Cu monitor foils. The γ, X spectra have been collected with 15-40% relative efficiency coaxial HPGe detectors, the α spectra with Si surface barrier and PIPS detectors, with resolutions of 27 and 17 keV (FWHM) respectively, and β spectra with a conventional liquid scintillation counting and spectrometry (LSCS) system, with Horrocks number capability and a higher-resolution LSCS with α/β pulse shape analysis (PSA) discriminator. Significant results from the present measurements and the relevant analysis are shown in Fig. 1, showing an α spectrum referring to the radionuclides produced.

In order to produce NCA ^{211}At/^{211g}Po for metabolic radiotherapy, two radiochemical separations of At radionuclides from Po by-products and from the Bi target, followed by quality control tests have been carried out. The first radiochemical separations adopted have been a classical "wet" method based on liquid/liquid extraction and the second a dry–distillation method developed by our research group, based on the differential sublimation of At radionuclides and Po radionuclidic impurities as a function of temperature (*i.e.* thermochromatography).

The radionuclidic purity of the different radiochemistry fractions produced from Bi target, ^{210}Po impurities and the final solution were also determined accordingly.
In Tab. 1 the experimental thick-target yields (TTY) obtained at LASA is compared with the calculated one (from 28.8 down to 20 MeV), both from the experimental microscopic data and from model prediction through the EMPIRE II code [15]; the discrepancies appear to be reasonable with regard to overall uncertainties, including the ones concerning the model parameterisation.

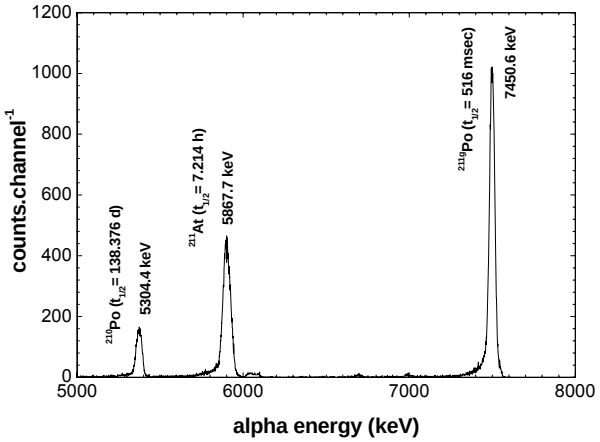

Fig. 1. α spectrum from thick Bi target irradiated with 32.8 MeV α-particles. These α spectra are relevant to the radiochemical purity performance of the final products.

Tab. 1. Experimental TTY (MBq·C^{-1}) measured in this work compared with the calculated ones obtained by integration of existing thin-target yield measurement fitting and of the model prediction by the EMPIRE II code.

1st Irrad. 28.8 MeV	experiment TTY	integrated TTY	Δ%	EMP II TTY	Δ%
^{211}At	8 085 ± 176	8 341	3.1	9 234	12.4

Regarding the production route of ^{186g}Re by (p,n) reaction on ^{186}W, a special effort has been brought up at LASA to deduce measured excitation functions starting from irradiation experiments on ^{nat}W at the, above mentioned MC40 cyclotron, with proton beam energy ranging from 7 to 16.5 MeV. In Fig. 2 the present results are compared with the previous literature ones and with nuclear model calculated curve obtained through EMPIRE II Code [15]. To obtain the NCA ^{18x}Re, a separation of the Re radioisotopes from irradiated W target, without any addition of either isotopic or isomorphous carrier was carried out. The selective radiochromatographic wet–chemistry method developed performs a very high radiochemical yield of > 98-99%.

The previous measurements of excitation functions for producing ^{64}Cu have been revisited, with main concern to γ spectrometry and radiation calibration aspects. The new experimental results are shown in Figs. 3 and 4.

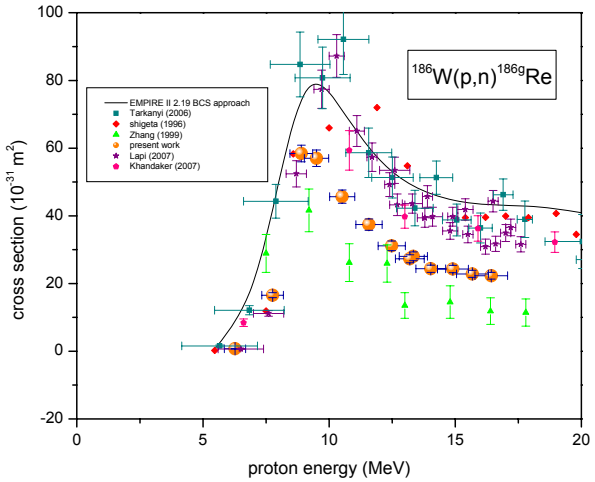

Fig. 2. New set of experimental cross-section (full circles) data for the ^{186}W(p,n)^{186g}Re reaction and the corresponding theoretical model calculation (full line).

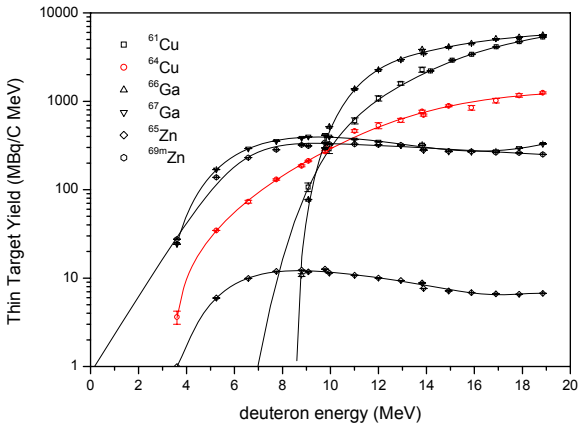

Fig. 3. Experimental thin-target yields obtained in this work for the different ^{nat}Zn(d,X) nuclear reactions.

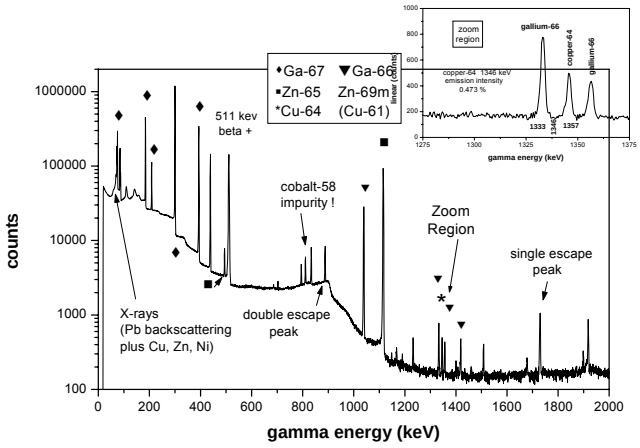

Fig. 4. Significant γ spectrum put in evidence in the energy region of interest. A special set up was used to detect accurately and precisely the very weak γ–line of ^{64}Cu at 1 364 keV [3].

NUCLEAR MODEL CALCULATIONS

The excitation function calculations have been carried out through the EMPIRE-II code system, developed by M. Herman, IAEA-NDS [15], accounting for the major reaction mechanisms for the various competing nuclear reaction channels, including the Optical Model (OM) and the full-featured Hauser-Feshbach model. Special care has been devoted to the model parameterisation, especially concerning the nuclear discrete level structure and the level density approach in the continuum, for both target and residual nuclei. When level density parameters could not be determined from the experiments, as for ^{186g}Re, the BCS approach was assumed. Particularly the Monte Carlo pre-equilibrium calculations have been successful in approximating the experimental values, in the case of proton induced reaction presently investigated.

Taking advantage from a long-time experience and activities in the field, the excitation functions were calculated for (α,2n) and (α,3n) reactions on ^{209}Bi target for the production of ^{211}At and ^{210}At, for ^{186}W(p,n) reaction for producing respectively ^{186g}Re and for ^{nat}Zn(d,X) and ^{64}Zn(d,2p) for production of ^{64}Cu as well.

RADIOCHEMICAL SEPARATIONS

Of course, in order of using the different RNs for labelling radiopharmaceutical compounds for both basic and applied research and applications onto humans for radiodiagnostics and/or metabolic radiotherapy purposes, it is necessary to set up selective radiochemical separations of the activated products from the irradiated targets: ^{64}Cu from ^{nat}Zn target and radioactive ^{66}Ga and ^{67}Ga by-products, ^{211}At/^{211g}Po from ^{209}Bi target and ^{210}Po radionuclidic impurities and ^{186g}Re from ^{nat}W and ^{186}W targets. The aim of these radiochemical separations is to obtain these radionuclides in very high specific activity chemical forms. As it is known from the updated IUPAC terminology and definitions, the specific activity A_S of a radioactive labelled compound is defined as: the ratio between the activity (Bq or more usually GBq) of the RN under investigation and the overall mass (kg or more usually μg) of all stable and radioactive nuclides of same Z in the same chemical form (*i.e.* A_S ranges typically from MBq.μg^{-1} up to TBq.μg^{-1}, while C_A is much less of several order of magnitude, i.e. MBq.g^{-1} to GBq.g^{-1}). The RNs obtained without voluntary addition of the *isotopic carried* are named NCA, according to international terminology (IUPAC, IUPAP, ISO, SI) [16-18].

Quality control/assurance tests have been carried out in order to assess the following purity parameters: radionuclidic (radioisotopic and non-radioisotopic) purity, radiochemical purity, chemical purity, specific activity A_S and radioactive concentration C_A (unfortunately, in non-specialised literature AS and CA are often interchanged even if their chemical-physical meaning is completely different). The biological purity of the labelled compounds was also investigated in order to the envisaged administration of the labelled compounds to either laboratory animals or human as final purpose.

CONCLUSIONS

As general remarks our previous results were partially compared with the ones discussed in the context of IAEA CRPs on the nuclear data for radiotherapeutic radionuclide production. Such a comparison gave reason for further deep investigations as by the present work.

AKNOWLEDGEMENTS

The present research work was funded in the mainframe of the Commission V of INFN (experiments COPPER-64, ASTATO and RHENIUM, 2001-2008) and the MIUR, Italy. Thanks are due to JRC-Ispra (EC) Cyclotron Laboratory for irradiating the samples and fruitful scientific discussions.

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