The modeling of the reaction cross sections in the production of teranositic radionuclides

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Abstract

We utilize various nuclear reaction codes with the aim to guide, interpret, and support the experiments in the proton-induced production measurements of radionuclides for the development of innovative radio-pharmaceuticals. The understanding of reaction cross sections at low-intermediate energies is crucial in this context and requires the knowledge of nuclear models available in different codes, such as EMPIRE, TALYS, and FLUKA. These nuclear reaction codes serve as tool to interpret the measurement of production cross-sections and to complete the measurements with estimates of production of contaminants and/or stable isotopes that are difficult to measure. We illustrate different model calculations to simulate isotope production useful in experiments devoted to the measurement of proton-induced production of the two theranostic radio-isotopes ^{67}Cu and ^{47}Sc.

Key words: *nuclear reactions; isotope production; copper 67; scandium 47; cross sections; simulation.*

La modelación de las secciones eficaces de reacción en la producción de radionúclidos teranosíticos

Resumen

Utilizamos varios códigos de reacción nuclear con el objetivo de guiar, interpretar y respaldar los experimentos en las mediciones de producción de radionúclidos inducidas por protones para el desarrollo de productos radio-farmacéuticos innovadores. La comprensión de las secciones eficaces de reacción en energías intermedias bajas es crucial en este contexto y requiere el conocimiento de modelos nucleares disponibles en diferentes códigos, como EMPIRE, TALYS y FLUKA. Estos códigos de reacción nuclear sirven como herramienta para interpretar la medición de secciones eficaces de producción y para completar las mediciones con estimaciones de producción de contaminantes y / o isótopos estables que son difíciles de medir. Ilustramos diferentes cálculos de modelos para simular la producción de isótopos útiles en experimentos dedicados a la medición de la producción inducida por protones de los dos isótopos teranósticos ^{67}Cu y ^{47}Sc.

Palabras clave: *reacciones nucleares; producción de isotopos; cobre 67; escandio 47; secciones eficaces; simulación.*

Introduction

The applications of radioisotopes are found in almost all country of the world, significantly contributing in the increase of health care, safety, and industrial developments. The amount of medical procedures involving the use of radioisotopes is constantly increasing worldwide, and these procedures require a growing number of different isotopes. In industry, the uses of isotopes are very diverse, and their impact in the various industrial sectors may differ greatly from sector to sector [1].

Within radionuclide therapy, the implementation of the concept of "theranostics", which refers to an integrated approach to diagnosis and therapy using suitable combinations of molecular targeting vectors and radionuclides, has started recently. A recent coordinated research activity promoted by IAEA [2] assessed that, amongst the most innovative and emerging radioisotopes for theranostic application, a special role is played by beta-emitters Copper-67, Scandium-47 (together with Rhenium-186, which is not discussed here). The production of these two radionuclides is the subject of the present study.

The isotope ^{67}Cu is a very promising candidate for theranostics due to the specific role of copper in several biochemical processes and it has been long considered an excellent nuclide for radioimmunotherapy [3]. Its relatively long half-life (T1/2 =61.83 h) permits to follow the slow biodistribution of antibodies, the most used bioactive vectors for 67Cu, while its β-- emission (mean Eβ-- = 141 keV) has a therapeutic effect of short-medium range on the targeted cells. The low energy γ-rays produced by ^{67}Cu -decay (Eγ = 184.58 keV, I = 48.6%) allow to follow its track and monitor tumor uptake during therapy, by using standard SPECT or SPECT/CT cameras developed for the 140 keV γ-rays of ^{99m}Tc. Also ^{47}Sc [4] is a very promising candidate for radio-nuclide therapy. It has desirable nuclear properties since it is a long-lived β-- emitter (T1/2 = 3.35 days, Eβ--(av) = 162 keV, main Eγ = 159.4 keV, I = 68.3%) with the γ-ray emission suited for diagnostic imaging procedures, using standard devices aready developed for ^{99m}Tc, as in the case of ^{67}Cu.

At INFN-LNL (Istituto Nazionale di Fisica Nucleare, Laboratori Nazionali di Legnaro, Italy), in the framework of the LARAMED (LAboratory of RAdionuclides for MEDicine) project, there has been a great deal of activities in the investigation of the best production routes, based on high-performance cyclotrons, of radionuclides with relevant medical interest. Related to this project, a new accurate measurement of the ^{68}Zn(p,2p)^{67}Cu excitation function in the energy range 35-70 MeV was recently completed in collaboration with the ARRONAX cyclotron facility in Nantes [5]. New data of the ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga cross sections were also obtained. Accurate knowledge of cross section is the first step in the development of optimization procedures for radioisotope production, and, in parallel to the experimental activities, it is of fundamental importance to carry out simulations and theoretical estimates, to direct the experiments towards the most promising routes for productions.

Another similar campaign of measurements started in 2017 to determine the production cross sections of ^{47}Sc, using enriched Titanium or Vanadium targets. Theoretical simulations are here needed to predict which target and in particular which Titanium isotope is the most promising route to produce ^{47}Sc with the highest purity. In the next section we describe the main ingredients and tools for the theoretical description of the production cross sections of the radionuclides of interest. Then in the subsequent section we discuss the results of the calculations performed, and in the last section we draw the conclusions.

Materials and methods

Theoretical tools.

The theoretical modeling of reaction cross-section for the production of radionuclides of pharmaceutical relevance is an important tool to interpret the production measurements and to guide the experiments towards the most promising production conditions (in terms of energy windows, target materials, isotopic varieties etc.). Modeling is also important for integrating the measurements with estimates of production rates of contaminants that are challenging to measure, including fast decay radionuclides or stable isotopes. Another possible future use of these modeling tools concerns the development of techniques for standardized production and quality control, as well as engineering advancements in the radionuclide production. For this purpose one should have access to validated nuclear reaction codes, to define the abundances of contaminants whenever these are too difficult to measure. To our knowledge, no current nuclear reaction code is presently ready for such validation, and the research activity herein described aims to assess the usability of widely available nuclear reaction codes for the scopes related to the production of radio-pharmaceuticals.

We have taken into consideration in the present study the nuclear reaction codes TALYS [6], EMPIRE [7], and FLUKA [8] analyzing their outcomes in the production of radionuclides. The cyclotron recently installed at SPES (INFN, Legnaro) ranges between 35 and 70 MeV, an energy interval covered by all three codes.

This region is dominated by the so called pre-equilibrium or pre-compound process, sometimes also called multi-step process. This is an intermediate reaction process between the two extremes characterized on one side by the statistical compound nucleus formation and on the other side by the direct processes.

Pre-equilibrium emissions occur after the first stage of the reaction but before statistical equilibrium of the compound nucleus takes place. During the pre-equilibrium phase, the motion of the incident particle gradually evolves into more complex states of the compound nucleus and the initial energy and momentum of the projectile is mediated by the nuclear medium. Pre-equilibrium processes describe a significant fraction of the reaction cross section for incident energies between 10 and (at least) 200 MeV.

In these codes, pre-equilibrium is described through a sequel of excitation steps where gradually more and more complex configurations of particle-hole excitations are accessed, with subsequent emission of particles. This description is known as exciton model and forms the basis for the calculation of the pre-equilibrium component in all these codes.

EMPIRE is a nuclear reaction code designed in a modular array, and contains a variety of nuclear models designed for calculations over a broad range of energies, targets, and incident particles. The energy range starts just above the resonance region in the case of a neutron projectile, and extends up to few hundred MeV for heavy-ion induced reactions. The code accounts for the major nuclear reaction models, such as optical model, Coupled Channels and DWBA, Multi-step Direct, Multi-step Compound, exciton model, hybrid Monte Carlo simulation, and the complete Hauser-Feshbach model including width fluctuations and the optical model for fission [7].

Also TALYS is a modular computer code for the analysis and prediction of nuclear reactions. Specifically, it simulates nuclear reactions that involve neutrons, photons, protons, deuterons, tritons, ^{3}He and alpha-particles, in the 1 keV - 200 MeV energy range and for target nuclides of mass 12 and heavier [6]. Amongst specific features of the TALYS package we recall the exact implementation of many of the latest nuclear models for direct, compound, pre-equilibrium and fission reactions and completely integrated optical model and coupled-channels calculations. In particular, the optical potential module incorporates recent parameterizations for many nuclei, both phenomenological (with the possibility of including dispersion relations) and microscopic (starting from the nucleon-nucleon interaction). In addition the code includes automatic reference to nuclear structure parameters as masses, discrete levels, resonances, level density parameters, deformation parameters, fission barrier and gamma-ray parameters, generally from the IAEA Reference Input Parameter Library, various width fluctuation models for binary compound reactions and, at higher energies, multiple Hauser-Feshbach emission until all reaction channels are closed, various phenomenological and microscopic level density models and, finally, modern models for pre-equilibrium reactions, and multiple pre-equilibrium reactions up to any order.

The last nuclear reaction code we take into consideration, FLUKA, is a general purpose Montecarlo code for modeling particle transport and interaction with matter. It also covers an extended range of applications, spanning from proton and electron accelerator shielding to calorimetry, dosimetry, detector design, radiotherapy and more. The main application of FLUKA is devoted to high-energy physics, but over the last years it has been widely employed also in medical physics applications in a lower energy regime, in particular in protontherapy and in the production of PET radioisotopes [9].

The FLUKA model at low energies, PEANUT (Pre-Equilibrium Approach to Nuclear Thermalisation), can be used to calculate the production of residual nuclei and in many cases the results are already validated with experimental data. Residual nuclei (and, thus, radionuclides) in FLUKA emerge directly from the inelastic hadronic interaction models and can be calculated for arbitrary projectile-target configurations (including nucleus-nucleus interactions) and energies [8].

Results and discussions

First we considered the production of the theranostic ^{67}Cu by irradiation of a ^{68}Zn target with a proton beam in the energy range 35-70 MeV. The interest in this reaction stems from the fact that a related experiment has been recently performed at the ARRONAX facility precisely in this energy range, with results published in Ref. [5]. We compared the measurements of this experiment with the results obtained with the three nuclear reaction codes (figure 1).

In figure 1 there are 4 model calculations: EMPIRE, FLUKA, TALYS, and TALYS*. TALYS*, differently from TALYS, does not use the default parameters/models but new, more modern theory models that are implemented in TALYS but not used with the default parameters. The set of parameters used in TALYS* were proposed in Ref. [10], by considering different nuclear reactions than those analyzed in this work. In particular in TALYS*, for pre-equilibrium reactions, numerical transition rates were considered in the exciton model, with collision probabilities extracted from the optical potential; moreover, the level densities were calculated microscopically (using a Skyrme force) from Hilaries's combinatorial tables [11].

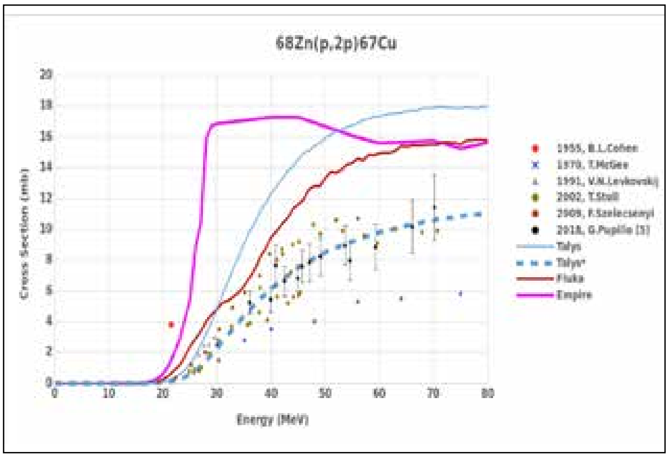

Figure 1. Theory vs experiments in the production of ^{68}Zn(p,2p)^{67}Cu. Experimental points with bars are from Ref. [5]. The other experimental points are for comparison with previous experiments (see Ref. [5] for details and References).

It is important to note that the set of parameters used in TALYS* calculations are taken from Ref. [10] and are not optimized for the specific reaction of interest reported in this work.

Next we consider the production of ^{47}Sc. Ref. [12] published recently a study of production of this radionuclide with the use of ^{51}V as target material. The authors also published EMPIRE and TALYS calculations; as expected, our results obtained by using default parameters are in agreement with the estimation reported in Ref. [12]. Considering the INFN project PASTA, presently ongoing in collaboration with ARRONAX facility with the scope of measuring the production of ^{47}Sc with enriched Titanium targets, in this work we consider Ti-48, Ti-49 and Ti-50 as target materials.

Given the cost of enriched materials and the typical limitations for the experimental projects (budget, time, etc) it is unfeasible to measure all possible nuclear reactions producing ^{47}Sc with proton beams and enriched titanium targets. For this reason, the different nuclear codes were used to estimate the course of the reactions ^{48}Ti(p,x)^{47}Sc, ^{49}Ti(p,x)^{47}Sc and ^{50}Ti(p,x)^{47}Sc. In all cases, the co-production of ^{46}Sc (a long-lived β^{--} emitter), the main contaminant radioisotope, is a crucial aspect that needs to be checked in view of the future radio-pharmaceutical use of ^{47}Sc. Figure 2 shows the predictions for radionuclide production with ^{49}Ti target, using the three codes. It has to be noted that there are no experimental data available for this reaction. Considering the medical application of ^{47}Sc, in figure 2 we illustrated a comparison of production of both ^{47}Sc and ^{46}Sc .

In figure 3 we predicted the ratio of the cross sections for the production of ^{47}Sc and ^{46}Sc by using ^{49}Ti (upper panel), and ^{50}Ti targets (lower panel). All the codes indicate that in the energy range 25-40 MeV the production of ^{47}Sc is most favorable with ^{49}Ti targets: the ratio varied from 8 to 28 (upper panel). With ^{50}Ti targets, as shown in the lower panel, the codes suggest the energy window between 40-70 MeV to favor ^{47}Sc production

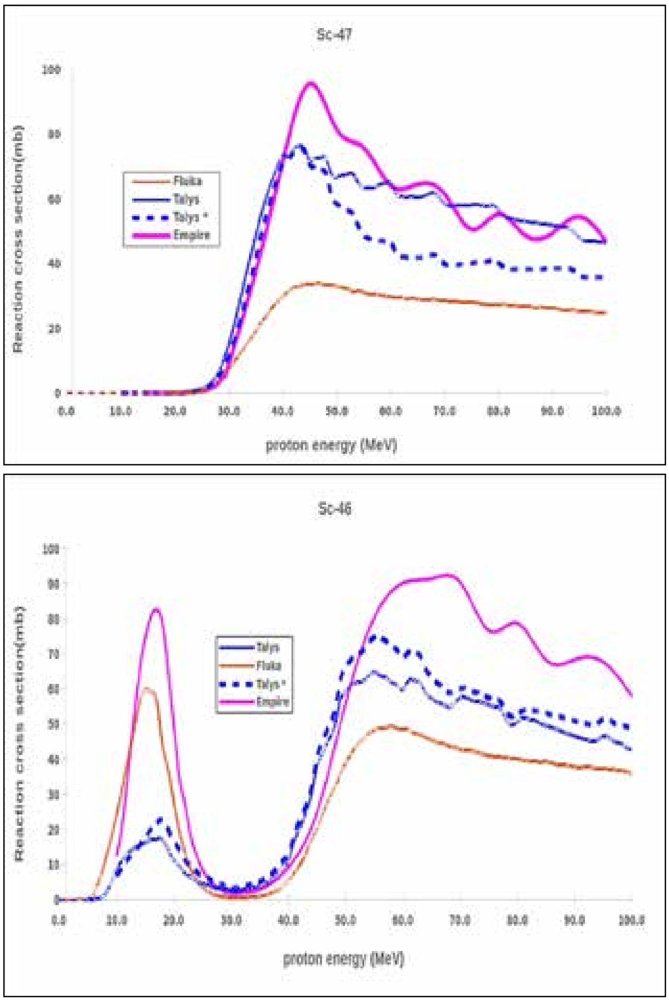

Figure 2. Theory prediction for ^{49}Ti(p,x)^{47}Sc (up) and ^{49}Ti(p,x)^{46}Sc (down) reactions. The curves illustrate results obtained with the three nuclear-reaction codes.

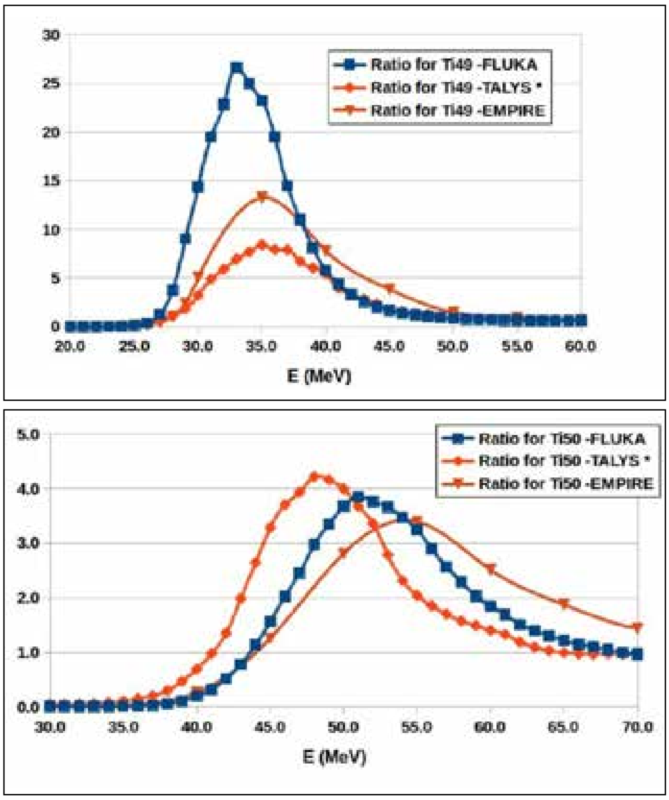

Figure 3. Prediction of the ratio of the production cross-section for ^{47}Sc over ^{46}Sc. Upper panel using enriched ^{49}Ti, lower panel with ^{50}Ti targets.

with lowest contamination by ^{46}Sc, with the ratio varying from 3.5 to 4.2. Considering the similar abundance of ^{49}Ti and ^{50}Ti (respectively 5.5% and 5.4%) and thus assuming a similar cost for these enriched materials, the investigation of the ^{49}Ti (p,x)^{47}Sc reaction may be more convenient than the ^{50}Ti (p,x)^{47}Sc one.

Conclusions

The new cross section data of the ^{68}Zn(p,x)^{67}Cu reaction, recently published [5], was compared with theoretical estimates obtained by public nuclear-reaction codes, TALYS, EMPIRE, and FLUKA. The study involved the production also of other radionuclides (^{66}Ga, ^{67}Ga, ^{64}Cu, ^{65}Zn) but we have limited ourselves here to ^{67}Cu only, for brevity. Overall, the codes produce comparable results, with estimates that can change easily by a factor of 2 between different calculations. A new variant of TALYS calculations, using the most modern TALYS modules in place of the standard ones, and denoted as TALYS*, appears to perform somewhat better than the others over the wide range of radionuclides considered.

As next step, we have used the predictions of the three reaction codes to guide the new PASTA experiment (funded by INFN) on the production of the theranostic ^{47}Sc radionuclide. If one uses enriched Titanium targets, the selection is amongst ^{49}Ti, ^{50}Ti, or ^{48}Ti. The isotope 48 is by far more abundant than the first two, with fractional abundances respectively of 5,5:5,4:73,8. But according to our simulations (not shown here for brevity) the target ^{48}Ti favors the production of the contaminant ^{46}Sc over the theranostic ^{47}Sc practically in the entire energy range 35-70 MeV, except at the lowest energy where the absolute yields are nevertheless very low and therefore not interesting. Isotopes ^{49}Ti and ^{50}Ti seem more promising since the predicted cross section for ^{47}Sc is larger than that for ^{46}Sc. The three codes predict that ^{49}Ti targets perform better than ^{50}Ti ones, since in all calculations the ratio theranostic/contaminant is larger. Also, the calculations suggest to consider the energy window 25-40 MeV to maximize that ratio. To our knowledge, no measurements of ^{49}Ti(p,x)^{47}Sc production have been published to date and this study points to the need to look into this production route as one of the most promising for cyclotron production of ^{47}Sc. It is foreseen that soon new measured data will be available with ^{49}Ti target, along with the PASTA project.

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