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Abstract
^{67}Cu and ^{47}Sc are theranostic radionuclides in the spot-light of the scientific community: the insufficient availability is limiting their use in clinical and pre-clinical studies. The aim of this work is the analysis of ^{67}Cu and ^{47}Sc production by using high-energy and high-intensity cyclotrons, by exploring promising nuclear reactions induced by proton-beams. In this work are presented the first measurement in the energy range 45-70 MeV of the ^{70}Zn(p,x)^{67}Cu, ^{64}Cu, ^{67}Ga, ^{66}Ga nuclear cross sections (outcome of the COME project), and the preliminary results of the ^{nat}V(p,x)^{47}Sc, ^{46}Sc, ^{44m}Sc, ^{44}Sc, ^{48}Sc, ^{43}Sc nuclear cross sections, investigated in the on-going PASTA project.

1 Introduction

The aim of this work is the analysis of ^{67}Cu and ^{47}Sc production by using high-energy and high-intensity cyclotrons, as the one installed at Legnaro National Laboratories of the Italian Institute of Nuclear Physics (INFN-LNL, Padua, Italy), in the framework of SPES project [1]. The SPES project is focused both on the use of Radioactive Ion Beams (RIB) and applied research in the field of nuclear medicine, through the LARAMED project – acronym of LAboratory of RAdionuclides for MEDicine. LARAMED infrastructure (beam-lines and laboratories) is currently under construction and the research activities regarding cross section measurements are carried out at the ARRONAX facility (Nantes, France) [2], where a 70 MeV cyclotron is operative. Among the radionuclides of major interest for the collaboration LARAMED-ARRONAX there are ^{67}Cu and ^{47}Sc, thanks to their great potential in theranostic applications, allowing the selection of patients with higher chance to respond to specific treatments and the application of individually customized dosimetry. The worldwide increasing interest on this topic is well-represented by the recent Coordinated Research Project (CRP), promoted by the International Atomic Energy Agency (IAEA), focused on "*^{67}Cu, ^{186}Re and ^{47}Sc as Emerging Theranostic Radionuclides*" [3]. The interest on ^{67}Cu- and ^{47}Sc-labelled radiopharmaceuticals stands on their physical characteristics (Table 1): the β^- particles of low-medium energy are useful to deliver cytotoxic dose to small-medium sized tumours while the emitted γ-rays are suitable for SPECT or SPECT/CT cameras; moreover, the relatively long half-life of ^{67}Cu and ^{47}Sc (about 2.6 d and 3.3 d respectively) permits to follow the slow biodistribution of monoclonal antibodies and specific molecular vectors, such as peptides, allowing their use also in radioimmunotherapy. The long half-life allows also centralizing the production, limiting the investment to be done. Finally, β^+ counterparts such as ^{64}Cu and ^{44}Sc exist and may also allow the theranostic approach to be used with PET imaging.

Nowadays, the insufficient availability of ^{67}Cu and ^{47}Sc is limiting their use in clinical and pre-clinical studies. The aim of this work is to study unexplored nuclear reactions to find out possible production routes for these emerging radionuclides. In view of an optimized production, the co-production of contaminant radionuclides, especially the isotopic impurities that cannot be chemically separated from the desired product and affect the RadioNuclidic Purity (RNP), is a key-point. For this reason, experiments are designed in order to measure not only the nuclear cross section of the radionuclide of interest (*e.g.* ^{67}Cu and ^{47}Sc), but also the production of isotopic contaminants (*e.g.* ^{64}Cu and ^{46}Sc) and other impurities (*e.g.* ^{67}Ga and ^{51}Cr) that may affect the radiochemical procedure aimed at the radionuclide extraction and purification.

Table 1: Nuclear data of interest extracted from NuDat database [4]

Radionuclide	*Half-life*	*γ-ray Energy (Intensity)*	*β⁻ Mean Energy (Intensity)*
^{67}Cu	61.83 h (*12*)	184.577 keV (48.7% *3*)	141 keV (100% *6*)
^{47}Sc	3.3492 d (*6*)	159.381 keV (68.3% *4*)	162.0 keV (100% *8*)

The COME project is focused on the first measurement of the ^{70}Zn(p,x)^{67}Cu nuclear reaction in the energy range 45-70 MeV, complementing the existing data up to 35 MeV [5-7]. Experimental evaluation of the ^{70}Zn(p,x)^{64}Cu, ^{70}Zn(p,4n)^{67}Ga and ^{70}Zn(p,5n)^{66}Ga reactions are also presented for the first time and compared with theoretical estimations provided by the TALYS code [8].

The PASTA project is focused on the production of ^{47}Sc by using proton beams (up to 70 MeV) and enriched metal targets of ^{48}Ti, ^{49}Ti, ^{50}Ti and ^{nat}V metal targets. Considering the high cost of the enriched metal powders, the collaboration with experts in nuclear codes such as EMPIRE, FLUKA and TALYS [9, 10, 8], is essential to compare the different nuclear reactions and identify the most promising energy region for ^{47}Sc production. In fact, no experimental data are available for the ^{49}Ti(p,x)^{47}Sc reaction, while only few measurements were performed with the ^{48}Ti and ^{50}Ti targets in oxide form [11, 5, 7]. Among the radionuclidic impurities of ^{47}Sc co-produced during the irradiation, ^{46}Sc (83.79 d) causes the major concern since it is the only radioisotope with a longer half-life than ^{47}Sc. For this reason, a cooling time after irradiation may only decrease the ^{47}Sc/^{46}Sc activity ratio: it is thus crucial to minimize as much as possible the ^{46}Sc production by carefully selecting the target material and the energy range. Aiming at this goal, the different nuclear codes were employed to estimate the cross sections to produce ^{47}Sc and ^{46}Sc by using the different target of interest (^{48}Ti, ^{49}Ti and ^{50}Ti).

2 Materials and Methods

Irradiation runs have been performed at the ARRONAX facility by using the proton beam with tunable energy 35-70 MeV and the stacked-foils method. Considering the use of enriched expensive materials, a dedicated target holder (Ø 11 mm), a graphite collimator (Ø 9 mm) and a plastic support have been designed and realized at the INFN-LNL workshop and used to precisely define the beam size on target during these irradiation runs. The duration of a typical run was 1.5 h with a constant current of about 100 nA, monitored during the bombardment by using an instrumented beam dump.

2.1 COME project

A typical stacked-foils arrangement was made of two identical patterns composed by an enriched ^{70}Zn target foil followed by a ^{nat}Al monitor foil. Enriched ^{70}Zn (> 95%) foils were realized by lamination at INFN-LNL Target Laboratory, starting from enriched metal powders, purchased by Trace Science International and Chemotrade. The ^{nat}Al foil is used to measure the effective beam flux by considering the reference reaction $^{nat}Al(p,x)^{24}Na$ recommended by IAEA [12] but also as catcher of possible recoil atoms from the target foil. Aluminium foils (0.5–1.0 mm thick) were in-between the two patterns to decrease the proton beam energy. An additional enriched ^{63}Cu (99.7%) thin metal foil is added at the end of the target arrangement to assure the production of the ^{61}Cu radionuclide, that is used as a tracer isotope of copper-elements in the separation process. In fact, the proton-irradiation of enriched ^{70}Zn produces a variety of radionuclides including ^{67}Ga (half-life 3.2617 d), that is of concern because it has a similar half-life of ^{67}Cu (about 2.6 d) and it decays to ^{67}Zn, as ^{67}Cu, thus emitting the same γ-lines [4]. Similarly to the previous with ^{68}Zn targets [13], also in this work we applied a radiochemical process aimed at the Cu/Ga separation to get an accurate measurement of ^{67}Cu and ^{67}Ga activity values by γ-spectroscopy. In view of the future need of reusing the enriched ^{70}Zn material through a dedicated recovery process, the chemical procedure is developed in order to separate also Cu and Zn elements. The efficiency of the chemical process is monitored for each irradiation run by using the tracer radionuclides ^{61}Cu, ^{66}Ga and ^{69m}Zn, respectively for copper, gallium and zinc elements. The chemical separation process (Figure 1), developed starting from the process described by [14], lasted approximately 4 hours and it is based on the following steps:

(a) removal of Ga isotopes by passing the radioactive target solution through a cation exchange resin AG50W-X4 hydrogen form, 100-200 mesh purchased from BioRad, Hercules (CA) USA, previously packed and conditioned in a glass column for chromatography: diameter 1.2 cm, height 20 cm;

(b) evaporation of the resulting solution to adjust the HCl concentration by a dedicated evaporation system, designed with acid fumes collection and neutralization;

(c) purification of Cu isotopes from zinc bulk by anion exchange resin AG1-X8 chloride form, 100-200 mesh purchased by BioRad, Hercules (CA) USA, previously packed and conditioned in a glass column for chromatography: diameter 1.2 cm, height 20 cm.

From the three final solutions named *xCu*, *xGa* and *xZn* (containing the three separate elements of interest Cu, Ga and Zn), three homogeneous aliquots of 5 ml each have been taken and analyzed by γ-spectrometry for the activity determination. The yield of chemical processing has been monitored for all target foils, by measuring the activity of the tracer radionuclides before and after the radiochemical procedure. All samples have been measured with the same high-purity germanium (HPGe) detector (10% relative efficiency, FWHM 1.0 keV at 122 keV, Canberra GC1020), previously calibrated with 5 ml reference liquid source (purchased to Cerca-Lea, France).

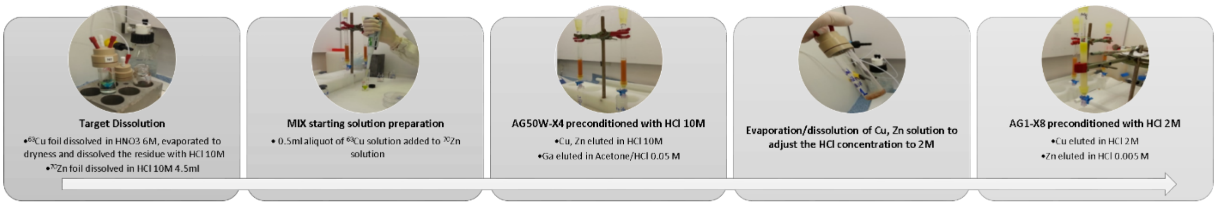

Fig. 1: Schematic description of the radiochemical process (left) and pictures of the key-steps of the radiochemical separation (right).

2.2 PASTA project

Generally, the accuracy of a cross section measurement is strongly related to the number of target atoms irradiated by the incident particles, making the characterization of the target a crucial issue. For this reason, metallic targets are more desirable than the oxide ones, whose accurate thickness and density are more difficult to measure. Since highly pure metal ^{nat}V foils are available commercially, the $^{nat}V(p,x)^{47}Sc$ reaction was measured first. On the contrary, enriched metal Ti-foils are not manufactured: these isotopes are usually available only in the oxide form while only few suppliers worldwide provide such materials in the metal powder form. Among the Ti-isotopes (abundance ^{48}Ti 73.72%, ^{49}Ti 5.41% and

^{50}Ti 5.18%), the priority was given to ^{48}Ti thanks to the achievable maximum enrichment and relatively low price. The enriched ^{48}Ti metal targets were realized by using the High energy VIbrational Powders Plating (HIVIPP) method [15], to homogeneously (>90%) [16] deposit the titanium powder on an aluminium support, as one of the deliverables of the *E_PLATE* project. Enriched ^{48}Ti metal targets were irradiated at the ARRONAX facility by using the stacked-foils technique (Figure 2); data analysis is on-going.

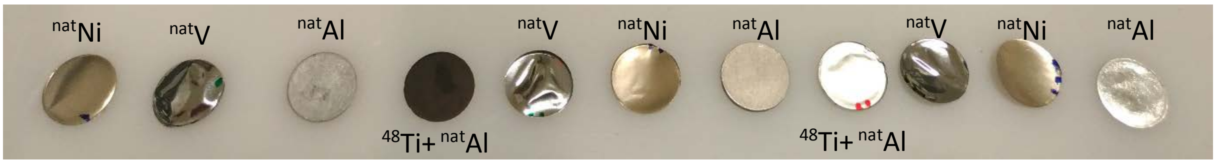

Fig. 2: Photograph of the stacked-foils target typically used in the PASTA project.

In order to optimize future irradiation runs on enriched ^{49}Ti and ^{50}Ti targets, the nuclear codes TALYS [8], EMPIRE [9], and FLUKA [10] were employed to estimate the trend of the nuclear reactions of interest, in particular the production of ^{47}Sc and ^{46}Sc. 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. Likewise, 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. The last nuclear reaction code we take into consideration, FLUKA, is a general purpose Monte Carlo code for modeling particle transport and interaction with matter. 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, such as proton therapy and production of PET radioisotopes. The FLUKA model at low energies, PEANUT (Pre-Equilibrium Approach to Nuclear Thermalization), can be used to calculate the production of residual nuclei (and, thus, radionuclides); in many cases the results are already validated with experimental data. Residual nuclei 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.

3 Results and discussion

3.1 COME project

Figures 3-7 reports the experimental data compared with theoretical results obtained by using TALYS nuclear code: *Talys 1*.9 refers to the default set of parameters [8], *Talys* * *1.9* refers to a new set of models proposed by [17] to run the TALYS code. In all cases, the results obtained in different irradiation runs show a regular trend of the ^{70}Zn(p,x)^{67}Cu, ^{64}Cu, ^{66}Ga, ^{67}Ga cross sections. No literature data are available for the energy range investigated in this work (45-70 MeV): when available, even if at lower energies, previous measurements are reported [5-7]; in case of the ^{70}Zn(p,α)^{67}Cu reaction (Figure 3), the recommended cross section by IAEA up to 40 MeV is also shown [18].

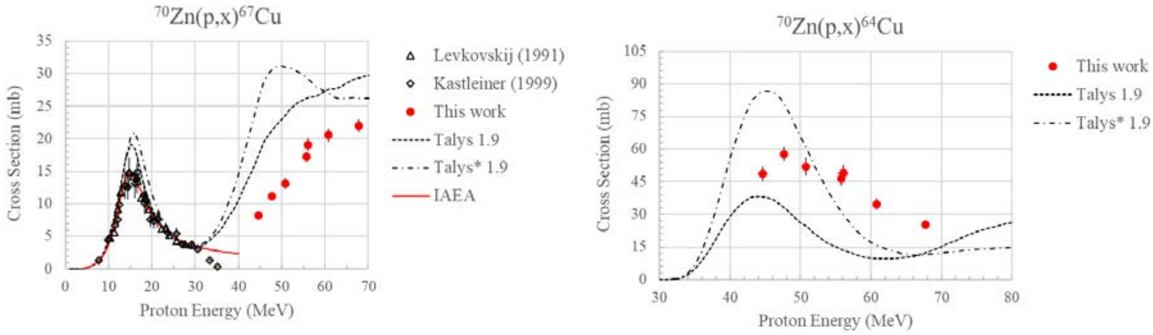

Fig. 3: Results obtained for the ^{70}Zn(p,x)^{67}Cu,^{64}Cu nuclear reactions; when available, previous measurements and IAEA recommended cross section are reported.

Experimental data of the ^{70}Zn(p,x)^{67}Cu nuclear reaction are reported in Figure 3 (left): in the investigated energy range (45-70 MeV) the cross section shows a regular increasing trend, that is properly described, even if overestimated, by the TALYS 1.9 code with default parameters. Figure 3 (right) reports the experimental data of the ^{70}Zn(p,x)^{64}Cu nuclear reaction, compared with TALYS estimations: both set of parameters do not properly describe the trend of measured values. Although the cross section values for ^{64}Cu production are always higher than those of ^{67}Cu, it has to be noted that the trend is decreasing for $E_P > 48$ MeV, whereas the ^{70}Zn(p,x)^{67}Cu reaction is increasing. The production of ^{64}Cu is of particular interest, because it is the only copper radionuclide that may affect the RNP of ^{67}Cu-labelled radiopharmaceuticals.

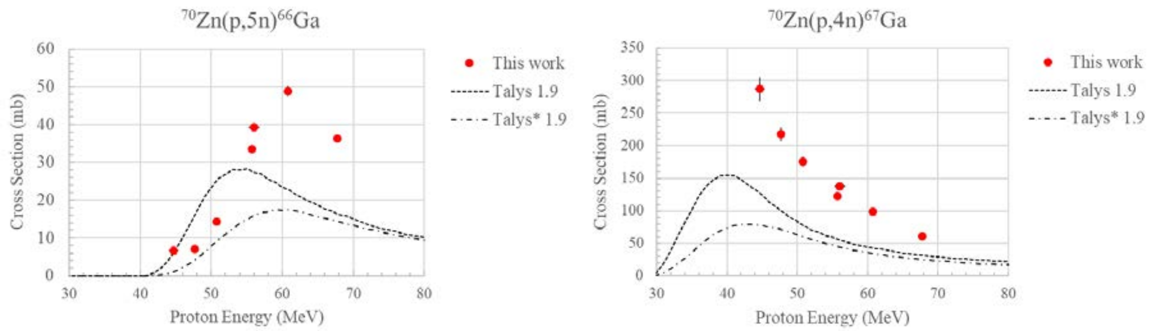

Fig. 4: Results obtained for the ^{70}Zn(p,x)^{66}Ga,^{67}Ga nuclear reactions.

The measurement of the cross section of the ^{70}Zn(p,5n)^{66}Ga and ^{70}Zn(p,4n)^{67}Ga nuclear reactions are shown in Figure 4 and compared with estimations by TALYS code. As in case of ^{64}Cu, theoretical estimations do not properly describe the trend of experimental data. The ^{70}Zn(p,5n)^{66}Ga reaction has a 50 mb peak at about 61 MeV, while the ^{70}Zn(p,4n)^{67}Ga reaction seems to have a peak at low energy (E_P < 45 MeV), whose value is not predictable without new dedicated irradiation runs at lower proton energies.

Figure 5 shows the new experimental data (red dots) with relative fit (red dashed line) obtained in this work for the nuclear reaction ^{70}Zn(p,x)^{67}Cu, compared with the recommended cross section by IAEA of the ^{70}Zn(p,α)^{67}Cu (red line) and ^{68}Zn(p,2p)^{67}Cu (blue line) reactions [18]. It is important to note that the cross section at 70 MeV on ^{70}Zn targets (about 22 mb) is double than the one on ^{68}Zn targets (about 11 mb). For this reason, the ^{67}Cu thick target yield in the energy range 45-70 MeV on 100% enriched ^{70}Zn is 39 MBq/µAh, nearly double than the one on fully enriched ^{68}Zn targets, i.e. 23 MBq/µAh. In order to estimate reasonable ^{67}Cu yield at EOB, a 62 hours irradiation run (equivalent to one ^{67}Cu half-life) is considered for both target materials: in case of ^{70}Zn the resulting ^{67}Cu activity is 1753 MBq/μA, i.e. 74% higher than the one with ^{68}Zn targets, that is equivalent to 1007 MBq/μA.

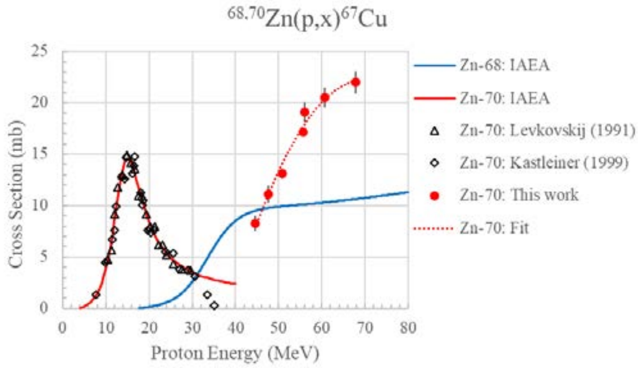

Fig. 5: Comparison of the nuclear reactions to produce ^{67}Cu by using enriched ^{70}Zn and ^{68}Zn target.

3.2 PASTA project

Data analysis on ^{48}Ti targets is still in progress. Preliminary results obtained of the $^{nat}V(p,x)^{47}Sc$, ^{46}Sc, ^{44m}Sc, ^{44}Sc, ^{48}Sc, ^{43}Sc are shown in Figures 6-7 (red dots) and compared with previous measurements [7]. In case of ^{43}Sc, the interference with the γ-ray at 373 keV emitted by ^{43}K was corrected; in case of ^{48}Sc, the nuclear cross section is calculated by considering the γ-rays at 175 keV and 1037 keV, in order to avoid the interference with ^{48}V at the 938 keV and 1312 keV γ-lines [4].

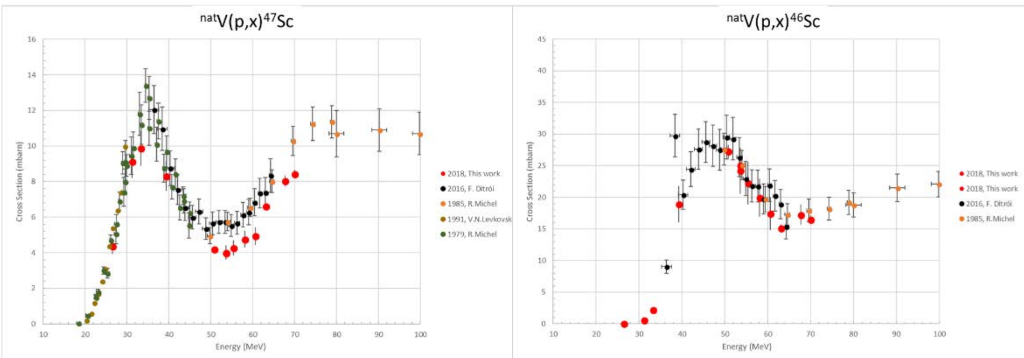

Fig. 6: Preliminary results obtained for the $^{nat}V(p,x)^{47}Sc$, ^{46}Sc nuclear reactions, compared with literature data [7].

In case of ^{47}Sc our experimental values are lower than the previous one in the energy range 50-60 MeV (discrepancy < 35%). On the contrary, in case of ^{46}Sc there is a good agreement with literature data in the entire energy range investigated (Figure 7); our measurements are the first near the threshold energy (E_{THR} = 17.6 MeV [4]), describing the initial trend of this cross section.

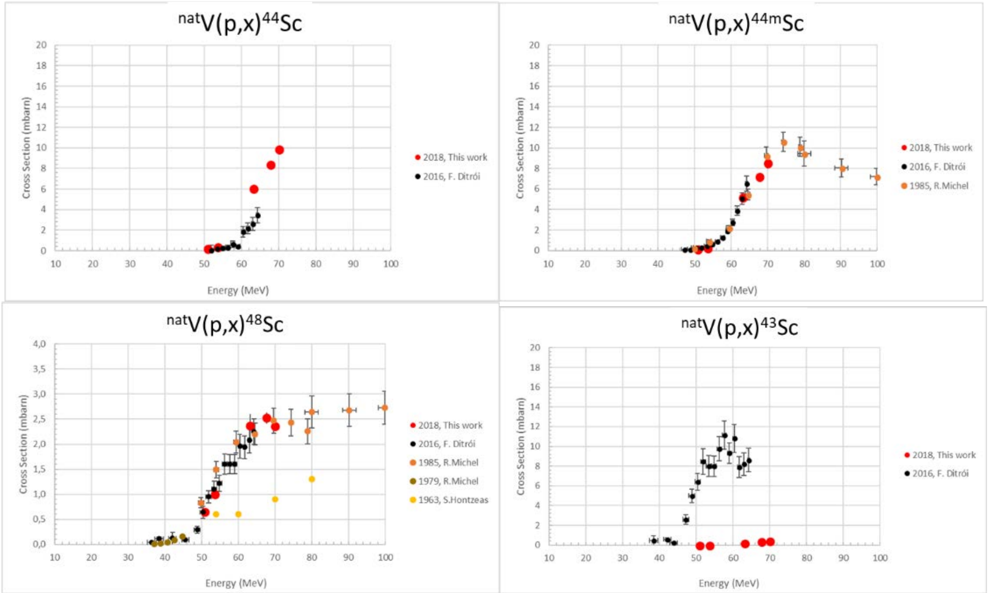

Fig. 7: Preliminary results obtained for the ${}^{nat}V(p,x)^{44m}Sc$, ${}^{44}Sc$, ${}^{48}Sc$, ${}^{43}Sc$ nuclear reactions, compared with literature data [7].

3.2.1 Theoretical estimations of the ${}^{47}Sc/{}^{46}Sc$ cross sections in case of ${}^{49}Ti$ and ${}^{50}Ti$ targets

Figure 8 reports the ratio of ${}^{47}Sc/{}^{46}Sc$ cross sections in case of ${}^{49}Ti$ and ${}^{50}Ti$ targets: results from FLUKA are plotted with a blue line, TALYS with a red line and EMPIRE with a brown line. It can be noted that all the nuclear codes indicate that for ${}^{49}Ti$ targets the most interesting energy region is 25-40 MeV, while in case of ${}^{50}Ti$ targets the best energy interval is 40-70 MeV. Considering the estimated value of ${}^{47}Sc/{}^{46}Sc$ cross sections ratio, *i.e.* 8-26 and 3.5-4.2 for ${}^{49}Ti$ and ${}^{50}Ti$ targets respectively, it results that the reaction on ${}^{49}Ti$ target provides a more favorable ${}^{47}Sc$ production in comparison with the one on ${}^{50}Ti$ targets.

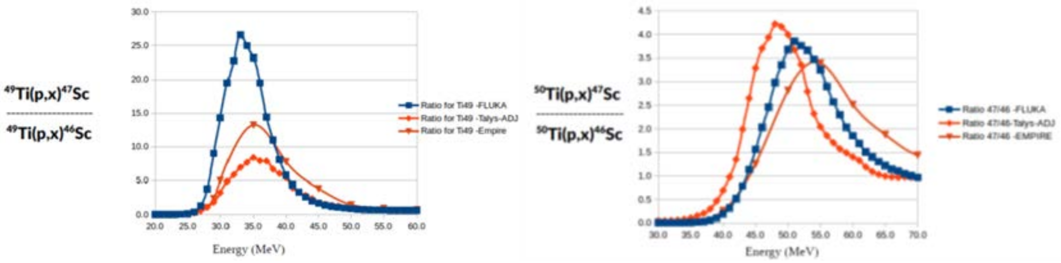

Fig. 8: Estimations of the ${}^{47}Sc/{}^{46}Sc$ cross section ratio in case of ${}^{49}Ti$ (left) and ${}^{50}Ti$ targets (right) performed by using FLUKA (blue line), TALYS (red line) and EMPIRE (brown line) codes.

4 Conclusion

This work describes the results obtained by COME and PASTA projects, performed in collaboration with the ARRONAX facility. The first cross section measurement of the ${}^{70}Zn(p,x){}^{67}Cu$, ${}^{64}Cu$, ${}^{66}Ga$, ${}^{67}Ga$ reactions in the energy range 45-70 MeV, by using highly enriched ${}^{70}Zn$ metal targets and a dedicated radiochemical procedure to separate Cu/Ga/Zn elements is presented. Results obtained in the COME project show that in the energy range 45-70 MeV the ^{67}Cu yield with ^{70}Zn targets is 74% higher than the yield obtained by using ^{68}Zn with same irradiation parameters. Preliminary results of the PASTA project, *i.e.* experimental data of the ^{nat}V(p,x)^{47}Sc, ^{46}Sc, ^{44m}Sc, ^{44}Sc, ^{48}Sc, ^{43}Sc nuclear reactions and theoretical estimations of ^{47}Sc/^{46}Sc ratio in case of ^{49}Ti and ^{50}Ti targets, are reported.

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