# OPTIMIZATION OF CONDITIONS FOR $^{67}$Cu PHOTONUCLEAR PRODUCTION

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Radiopharmaceuticals based on the $^{67}$Cu isotope have found wide use in immunotherapy. The present paper analyzes the conditions of $^{67}$Cu production by the $^{68}$Zn(γ,p) $^{67}$Cu reaction at an electron accelerator in relation to the target isotope and hot impurities yield, as well as the radiation risks. Consideration has been given to some variants of the technological target 40 g in weight made from natural zinc, and one enriched up to 99% in the $^{68}$Zn isotope. The target exposition to bremsstrahlung with end-point energy 30 and 60 MeV was studied. It has been found that the use of enriched target results in reduction of both the radiation risk (down to $10^{-4}$) and the scope of waste handling procedures.

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## INTRODUCTION

Nowadays**,** commercial isotope production is mainly based on the use of nuclear reactors (see, e.g., ref. [1]). However, the fission of $^{235}$U results in the production of side radioactive products, thereby giving rise to the problem of long-lived radioactive waste. Besides, the use of highly enriched $^{235}$U is connected with the danger of its uncontrolled proliferation.

An alternative method of radioisotope production lies in the use of heavy-particle/electron accelerators. Thus, $^{67}$Cu, as one of the most promising isotopes for radiotherapy of tumors by monoclonal antibodies, can be produced in the reactions under the action of neutrons, protons, α-particles, and also, high-energy photons. It has been demonstrated in ref. [2] that the photonuclear technology using the reaction $^{68}$Zn(γ,p)$^{67}$Cu provides the best conditions for the desired isotope production with regard to its total yield and the radionuclide-impurity production, even if a target made from natural zinc is used.

The major sources of isotope production hazards originate from radiation of the target isotope, hot impurities, and also target device elements. The individual risk $r$ of stochastic effects occurrence due to personnel irradiation is given by the relation $r=r_{\varepsilon}D$, where $D$ is the individual absorbed dose, and $r_{\varepsilon}$ is the total death risk factor due to radiation, taken to be $5.6\cdot10^{-2}$ events per 1 man·Sv for professional irradiation. By international practice, the boundary value of the individual risk of personnel irradiation is taken to be $10^{-3}$ per annum [3].

The present paper is concerned with the sources and levels of radiation risks, and also, with the ways of their reduction under $^{67}$Cu producing at an electron accelerator.

## 1. MAIN REACTIONS

At activation of a zinc target of natural isotopic composition ($^{64}$Zn – 48.6%, $^{66}$Zn – 27.9%, $^{67}$Zn – 4.1%, $^{68}$Zn – 18.8%, $^{70}$Zn – 0.6%) in the mixed X,n-radiation field, the yield of $^{67}$Cu and hot impurities, which give the main dose-forming contribution to the target radiation, goes by the reactions:

$^{68}$Zn (γ,p) $^{67}$Cu, $^{67}$Zn (n,p) $^{67}$Cu,
$^{64}$Zn (γ,2n) $^{62}$Zn, $^{64}$Zn (γ,n) $^{63}$Zn,
$^{70}$Zn (γ,n) $^{69m}$Zn, $^{68}$Zn (n,γ) $^{69m}$Zn,
$^{64}$Zn (n,p) $^{64}$Cu, $^{66}$Zn (γ,np) $^{64}$Cu,
$^{66}$Zn (γ,n) $^{65}$Zn, $^{64}$Zn (n,γ) $^{65}$Zn.

In the subsequent calculations, the maximum $^{67}$Cu activity of the natural zinc target by EOB was put to be $3.7\cdot10^{9}$ Bq (100 mCi). The concomitant radionuclide activity data required for estimating the radiation risks were obtained from the experiments at an 36 MeV electron accelerator when irradiating the 40g natural zinc target in the (240 μA; 10 h) run. The data on the $^{63}$Zn yield were obtained by calculations using the following formula

$$N = N_0 \int_{E_{th}}^{E_{\gamma\max}} \sigma(E_\gamma)\, f(E_{\gamma\max}, E_\gamma) dE\,, \qquad (1)$$

where $N_{0_}$is the number of nuclei of the initial isotope, $\sigma(E_\gamma)$ is the reaction cross section as a function of γ-quantum energy $E_\gamma$ , $E_{th}$ is the reaction threshold, $E_{\gamma\max}$ is the end-point energy of the bremsstrahlung spectrum, $f(E_{\gamma\max,}\, E_\gamma)$ is the function describing the X-ray spectrum (computed with the use of the GEANT 4 package [4]).

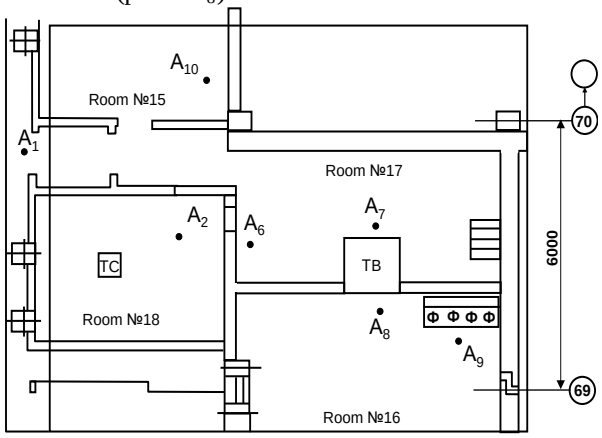
## 2. $^{67}$Cu PRODUCTION PROCESS AT THE "ACCELERATOR" Sc&R Est, NSC KIPT

**2.1.** By the end of target irradiation at an accelerator, the contribution of short-lived ($^{66}$Cu, $^{68}$Cu, $^{69}$Cu,$^{63}$Zn, $^{69}$Zn) and long-lived ($^{65}$Zn, $^{69}$Zn, $^{62}$Zn, $^{63}$Zn, $^{64}$Cu) radionuclides to the overall level of target radiation is hundreds times higher than the $^{67}$Cu radiation level. Besides, in the process of decay, the short-lived radionuclides emit high-energy gammas, and that necessitates a substantial increase in the radiation shield thickness. Therefore, for the decay of short-lived isotopes, the irradiated target must be cooled in the accelerator vault. The optimum cooling period for natural target is determined mainly by decay of the $^{62}$Zn, $^{63}$Zn isotopes, and makes 3 to 12 hours.

After cooling, the target is delivered by means of a pneumatic tube from the accelerator vault to a transport container (TC) situated in a room above the vault. Then, by using an electric hoist, TC is transferred to an inlet box of the radiochemical laboratory.

**2.2.** The layout of the laboratory including the rooms and locations of the target on its way from TC to a tech-

nological box TB (the points $A_1$, $A_2$, $A_6$, $A_7$,) is shown in Figure. The irradiated sample from TC is remotely discharged to a stationary box TB having iron and lead walls, where all the procedures of the $^{67}$Cu extraction are carried out (point $A_8$).




*Layout of the radiochemical laboratory with the reference points*

The radiation level near the TB surface is determined by the activity of the target being inside, and also, by a liquid radioactive waste (LRW) tank, located at the bottom of the box. The tank is filled weekly with LRW within one to three month period.

**2.3.** The specified permissible level of the equivalent dose rate (EDR) at the NSC KIPT makes 8.2 μSv/h. The expected EDR value was calculated at the following points of the plant (see Figure):

$A_1$ – the point near the transport container in the corridor;

$A_2$ – the point in a receiving chamber (room No 18);

$A_6$ – the point near the chamber for transporting the irradiated sample to the technological box (room No 17;

$A_7$ – the point behind the technological box (room No 17);

$A_8$ – the work seat before the technological box for operation with the $^{67}$Cu isotope (room No 16);

$A_9$ – the work seat before the $^{67}$Cu prepackage device PD (clean room №16);

$A_{10}$ – the LRW tank.

## 3. ANALYSIS OF ISOTOPE CONTRIBUTION TO EDR

The relationship between the absorbed dose rate caused by a point gamma source at a distance R, and the source activity M, expressed in mCi, is determined by the formula [3]:

$$\dot{D} = 2.35M \cdot K_\gamma / R^2, \ \mu Gy/sec = 8.46M \cdot K_\gamma / R^2, \ mGy/h, \quad (2)$$

where $K_\gamma$[roent·cm$^2$/(h·mCi)] is the specific gamma-ray constant, which shows the exposition dose rate produced by the 1 mCi point γ-source at a distance of 1 cm for 1 hour. The refined values of the specific γ-ray constants for each radionuclide were calculated with due regard for its radiation spectrum and the number of gammas per 1 decay according to a BNL database [5]. The results are given in the Table 1. Since the quality factor of the 0.1 to 2 MeV gammas is equal to 1, then the equivalent dose H can be considered equal to the absorbed dose D.

As it is evident from the Table 2, with consideration for the decay rate of the $^{67}$Cu and impurities, it is desirable that the process operations should be performed, as expected, no sooner than 3 hours after irradiation. Then the $^{62}$Cu, $^{66}$Cu, $^{68}$Cu and $^{69}$Cu isotopes, having the half-life less than 10 minutes, would not contribute to the target radiation.

At the $^{67}$Cu separation, other copper isotopes will be presented in the extract also. In particular, $^{64}$Cu ($T_{1/2}$=12.7 h) will transform to $^{64}$Ni. The concentration of $^{64}$Ni and $^{62}$Ni is expected to be comparable with the $^{67}$Cu content. In turn, the ratio of the $^{67}$Cu and $^{63}$Cu nuclei in the extract was calculated by formula (1) accounting the percentage of the initial nuclei. The ratio was found to be 0.042 and 0.062 at an electron energy of 30 and 60 MeV, respectively. Taking into consideration the contributions of other reactions with the final-state copper isotopes, the ratio of the of $^{67}$Cu nuclei to the rest copper isotopes will be still less.

At a $^{67}$Cu activity of 0.52 Ci and the target enriched in $^{68}$Zn up to 99%, as well as other conditions being hold true, the EDR value, $\dot{H}$, determined by the $^{67}$Cu radiation, will be equal to 298 μSv/h. The contribution from $^{65}$Zn will be less than 0.25 μSv/h, and it may be neglected. The $^{63}$Zn ($T_{1/2}$=38.1 min.) contribution just after EOB will be ~18 μSv/h. 3 hours later it will be 0.75 μSv/h. The contribution of other isotopes will be still less, and it may be also disregarded.

As the gamma-radiation of the target includes many lines, to simplify the calculations, it is reasonable to unite the adjacent lines. From consideration of the intensity and energy of the gammas (see Table 2), it is apparent, that the lines of the $^{64}$Cu, $^{63}$Zn, $^{65}$Zn isotopes with energy 1 to 1.5 MeV (20.8 % of radiation power) can be joined into one line, $E_{\gamma 1}$=1.2 MeV. The lines of $^{64}$Cu, $^{63}$Zn, $^{62}$Zn, $^{65}$Zn, $^{69}$Zn with energies between 0.4 and 0.7 MeV (75.7 % of radiation power) can be joined into the other line, $E_{\gamma 2}$=0.55 MeV. In this case, the radiation of $^{67}$Cu and the impurities with energy between 0.091 and 0.185 MeV, is no more than 3.5%.

Table 3 lists the values of EDR ($\dot{H}$, μSv/h) behind the lead (iron) shield of thickness *d* at points $A_i$ (see Figure), contributed by the 100 mCi $^{67}$Cu source based on the irradiated target from natural zinc, and also by the 0.52 Ci source based on the irradiated target made from 99% $^{68}$Zn-inriched material. In our calculations, the coefficients U and T, which characterize the protective barrier type and the personnel occupancy in the given rooms, were taken from paper [6, 7] and put to equal 1. The operations with the natural target are assumed to be performed in 3 hours after irradiation.

It is anticipated that the process of the $^{67}$Cu isotope production and the transfers of the irradiated target will be performed once for every week. In this case the average dose received by an operator is estimated to be $H_{av}$= H($A_{1)}$+H($A_{2)}$)+H($A_3$)+H($A_6$)+H($A_7$) = 0.02+15.6 + 0.4+8=24 μSv. This being within the established limit (Table 4).

*Table 1*

*Isotope composition of irradiated Zn- target and their gamma-ray constant*

| Isotope | $E_\gamma$ (MeV) | Number of gammas per one decay | Gamma-ray constant $K_{\gamma i}$, Roent $cm^2/h \cdot mCi$ | γ-radiation composition, % |
|---|---|---|---|---|
| $^{67}Cu$ | 0.091 | 0.22 | 0.09 | 0.57 |
| | 0.093 | 0.57 | 0.25 | 1.58 |
| | 0.185 | 0.22 | 0.21 | 1.33 |
| $^{64}Cu$ | 1.34 | 0.005 | 0.04 | 0.26 |
| | 0.51 | 0.38 | 1.16 | 7.37 |
| | | | | |
| $^{62}Zn$ | 0.041 | 0.25 | - | - |
| | 0.507 | 0.15 | 0.47 | 2.98 |
| | 0.51 | 0.17 | 0.54 | 3.43 |
| | 0.548 | 0.15 | 0.47 | 2.98 |
| | 0.596 | 0.26 | 0.82 | 5.21 |
| $^{63}Zn$ | 0.51 | 1.85 | 5.54 | 35.18 |
| | 0.669 | 0.085 | 0.36 | 2.29 |
| | 1.412 | 0.008 | 0.06 | 0.38 |
| | 0.961 | 0.07 | 0.43 | 2.73 |
| | | | | |
| $^{65}Zn$ | 0.51 | 0.031 | 0.15 | 0.95 |
| | 1.115 | 0.50 | 2.7 | 17.14 |
| $^{69m}Zn$ | 0.439 | 1 | 2.45 | 15.56 |
| | 0.574 | 0.03 | 0.01 | 0.06 |

*Table 2*

*Partial activity of the isotopes and EDR from the irradiated Zn- target (R=0.9 m, unshielded)*

| Isotope | Half-life | Target activity, mCi | | EDR, μSv/h | | | |
|---|---|---|---|---|---|---|---|
| | | | | By the EOB | | 3 hours after EOB | |
| | | Natural | Enriched | Natural | Enriched | Natural | Enriched |
| $^{67}Cu$ | 62.86 h | 100 | 520 | 57.4 | 298.7 | 55.5 | 289 |
| $^{65}Zn$ | 243 days | 24.3 | 0.085 | 72.3 | 0.25 | 72.3 | 0.25 |
| $^{69m}Zn$ | 13.7 h | 18.3 | | 46.8 | | 40.2 | |
| $^{62}Zn$ | 9.26 h | 186.6 | | 386 | | 308 | |
| $^{64}Cu$ | 12.7 h | 99.8 | | 125.1 | | 106.2 | |
| $^{63}Zn$ | 0.635 h | 1100 | 3.8 | 7340 | 19 | 278 | 0.72 |
| Σ | | 1529 | 523.9 | 8023 | 318 | 853 | 290 |

*Table 3*

*EDR produced by the $^{67}Cu$ source behind lead (iron) shield of thickness d at reference point $A_i$ ( 00 and 03 hours after irradiation)*

| Point | $d_{Pb,\ cm}$ | $d_{Fe,\ cm}$ | R, m | 100 mCi $^{67}Cu$, natural Zn | | EDR μSv/h 0.52 Ci $^{67}Cu$, enriched Zn |
|---|---|---|---|---|---|---|
| | | | | EDR (00), μSv/h | EDR (03), μSv/h | |
| $A_1$ | 14 | | 0.9 | 0.4 | 0.033 | <0.01 |
| $A_2$ | 14 | | 0.5 | 1.3 | 0.1 | <0.01 |
| $A_7$ | | 6 | 0.9 | 774 | 91.6 | <0.01 |
| $A_8$ | 5 | | 0.9 | 51 | 3.9 | <0.01 |
| $A_6$ | 5 | | 0.5 | 165.2 | 12.7 | <0.01 |
| | 9 | | | 15.8 | 1.23 | <0.01 |
| | 7 | | | 47.6 | 3.73 | <0.01 |

*Table 4*

*Estimates of EDR being received by different organs of the operator at distance R during $^{67}Cu$ packing procedures*

| Point | $d_{Pb,\ cm}$ | Organ, R, m | EDR, μSv/h | |
|---|---|---|---|---|
| | | | Natural zinc, 100 mCi | Enriched zinc, 0.52 Ci |
| $A_9$ | 1 | eyes, 0.5 | 1 | 5.2 |
| | | bone marrow, 0.4 | 1.5 | 7.8 |
| | | gonads, 0.4 | 1.5 | 7.6 |
| | | hands, 0.08 | 37 | 1.9 |
| $A_9$ | 1.5 | eyes, 0.5 | 0.08 | 0.4 |
| | | bone marrow, 0.4 | 0.12 | 0.6 |
| | | gonads, 0.4 | 0.12 | 0.6 |
| | | hands, 0.08 | 3 | 15 |

## 4. ESTIMATION OF RADIATION SHIELD OF THE LRW TANK

Table 5 gives the main isotopic composition and the partial activities of impurities in the water phase waste after the $^{67}$Cu extraction from the natural zinc-based target (12 hours after irradiation). The table gives also the dependence of the water drain on the period of its staying in the LRW tank. The next to last column of the table gives the partial activity of the weekly drain to the waste water phase, and the last column shows the maximum radiation level at a distance of 0.9 m from the LRW tank.

*Table 5*

*Activity of isotopes produced in one drain run in 1, 2, 3 and 4 weeks after irradiation of natural zinc target, and the maximum radiation from the LRW tank three months later, at a distance of 0.9 m without shielding*

| Isotope | Target activity after $^{67}$Cu extraction | 1st week after drain, mCi | 2nd week after drain, mCi | 3rd week after drain, mCi | 4th week after drain, mCi | Maximum activity in the LRW tank, mCi | Maximum EDR of the LRW tank μSv/h |
|---|---|---|---|---|---|---|---|
| $^{65}$Zn | 24.28 | 23.84 | 23.36 | 22.9 | 22.44 | 260 | 787 |
| $^{69m}$Zn | 16.92 | 0.002 | $4\cdot10^{-7}$ | - | - | 16.92 | 43.3 |
| $^{63}$Zn | 0.007 | $4\cdot10^{-4}$ | - | - | - | 0.007 | 0.043 |
| $^{62}$Zn | 149.2 | $3.8\cdot10^{-4}$ | - | - | - | 149.2 | 308.4 |
| Σ | 190.4 | 23.842 | 23.36 | 22.9 | 22.44 | 426.1 | 113.8 |

The thickness of the LRW tank shield was calculated in the same way like the calculation of the technological box shield. In view of change in the isotope activity ratio and the radiation spectra of the drain water phase, all radiation lines can be united into two lines, namely, 1.12 and 0.55 MeV. It is shown, that the required shield thickness is determined by the intensity of the nearby lines with $E_\gamma$ =1.12 MeV, and is found to be 9 cm of lead. For the averaged 0.55 MeV line, the shield thickness will be 3.7 cm, and it can be disregarded. So the LRW tank must be discharged once in every week. Then the maximum EDR caused by the 1.12 MeV gammas at a distance of 0.9 m without shielding will be 71 μSv/h. In this case, the necessary attenuation factor will make up 17. The lead thickness of 5 cm will be sufficient to provide the EDR value no higher 4.1 μSv/h.

## CONCLUSIONS

At treatment of the photonuclear target from natural zinc with 100 mCi activity in $^{67}$Cu, the technological box shield made from lead 5 cm thick (or 6 cm thick iron), as well as the 5 cm lead shield of the LRW tank provide the radiation environment, which meets standard requirements. On the first day of the week production cycle, when performing procedures to transport the container with the irradiated target, and also, to extract $^{67}$Cu, the operator will receive a dose of 24 μSv. In subsequent four days, the average daily dose will make up 5.5 μSv, and the total annual dose will be 1.26 mSv. That is much less than the permissible dose limit of 20 mSv. Under those conditions, the radiation risk will be no more than $7\cdot10^{-5}$.

In the case of the enriched zinc target of the same weight with activity 520 mCi, provided by the same irradiation mode, the dose received by the operator during packing will be distributed as follows: 4.3 μSv/day for bone marrow and gonads, and 110 μSv/day for hands (at a norm of 340 μSv/day).

With increase up to 2 cm in the lead thickness of the container for the separated $^{67}$ Cu product, the dose obtained by the hands will be decreased down to 8.5 μSv/day, and the radiation risk will amount $5.6\cdot10^{-5}$.

At the use of the enriched target, the productivity of $^{67}$Cu is by a factor of 5.2 higher than that for a target of natural composition. Considering that 1 gram of enriched $^{68}$Zn and one hour of the accelerator operation cost $500/g and $200/hour, respectively, the increase in the yield of the target isotope for a 30-hour cycle will fully compensate the cost of the target of enriched composition.

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## ОПТИМИЗАЦИЯ УСЛОВИЙ ФОТОЯДЕРНОГО ПРОИЗВОДСТВА $^{67}$Cu

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Радиофармпрепараты на основе изотопа $^{67}$Cu широко используются в иммунотерапии. В сообщении проанализированы условия его производства на ускорителе электронов по реакции $^{68}$Zn(γ,n)$^{67}$Cu в отношении выхода целевого продукта, а также горячих примесей и радиационных рисков. Рассмотрены варианты технологической мишени массой 40 г из цинка природного состава и обогащенного до 99% по изотопу $^{68}$Zn, активированной тормозным излучением с граничной энергией 30 и 60 МэВ. Показано, что при использовании обогащенной мишени радиационный риск снижается до $10^{-4}$, а также значительно уменьшается объем процедур с отходами.

## ОПТИМІЗАЦІЯ УМОВ ФОТОЯДЕРНОГО ВИРОБНИЦТВА $^{67}$Cu

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Радіофармпрепарати на основі ізотопу $^{67}$Cu широко використовуються в імунотерапії. У повідомленні проаналізовані умови його виробництва на прискорювачі електронів за реакцією $^{68}$Zn(γ,n)$^{67}$Cu відносно виходу цільового продукту, а також гарячих домішок і радіаційних ризиків. Розглянуто варіанти технологічної мішені масою 40 г із цинку природного складу і збагаченого до 99% за ізотопом $^{68}$Zn, активованою гальмівним випромінюванням із граничною енергією 30 і 60 МеВ. Показано, що при використанні збагаченої мішені радіаційний ризик знижується до $10^{-4}$, а також значно зменшується обсяг процедур з відходами.