

# ISOTOPE PRODUCTION WITH CYCLOTRONS

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## Abstract

In the last two decades cyclotron produced isotopes have gained increasing importance in nuclear medicine diagnosis. The lecture will cover aspects on target technology with regard to production efficiency, quality, reliability and automation. The production methods for the most commonly used radionuclides will be described. An example for two routine production systems based on gas target technology for I-123 and Rb-81/Kr-81 are presented.

## 1. INTRODUCTION

Modern isotope production facilities consist of a compact  $H^-$  cyclotron (Fig. 1) in the energy range between 10 MeV and 30 MeV with extracted currents up to 350  $\mu A$  [1] and a highly sophisticated target technology and chemistry [2].

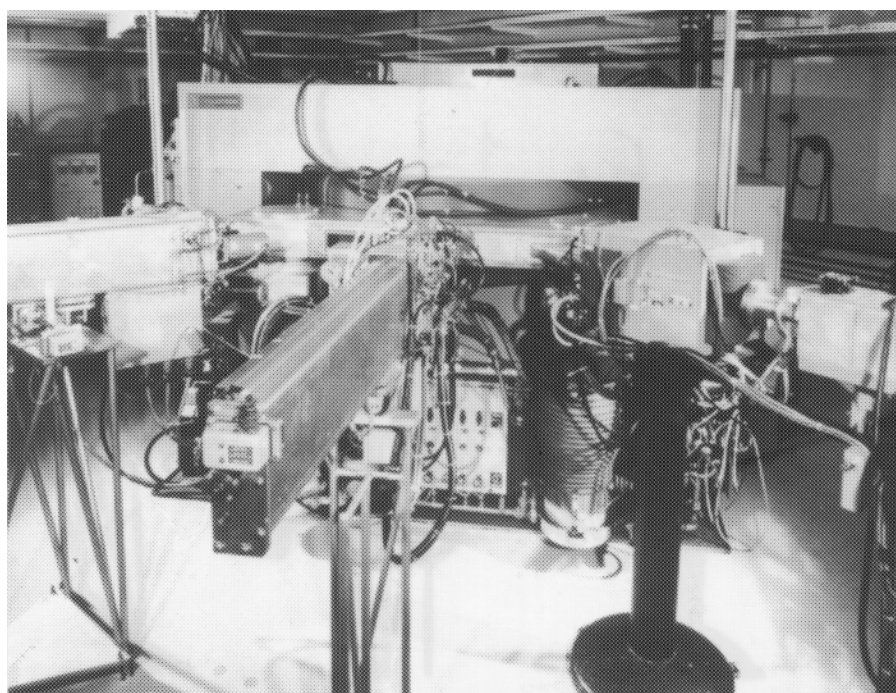


Fig. 1 Compact  $H^-$  cyclotron built by Cyclotron Cooperation, USA

The radioisotopes produced for medical applications are used in nuclear medicine for diagnosis. In contrary to X-ray studies where only static information can be obtained, nuclear medicine provides dynamic information and hence allows time-dependent studies of the function of organs. The labelled biomolecules and the radioisotopes involved should have the following ideal characteristics:

- no  $\beta^-$  particle
- short effective half-life
- $\gamma$ -energy in the range between 100 and 300 keV.

The above characteristics result in a maximum efficiency in the diagnosis and a minimum radiation dose to the patient. For example, Fig. 2 shows a comparison between I-131 and I-123. The physical properties show that the cyclotron produced I-123 ( $\gamma$ -energy 159 keV; no  $\beta^-$ ; short half-life) is more favourable than the reactor produced I-131 ( $\gamma$ -energy 364, 637;  $\beta^-$ -emission, long half-life) for use in nuclear medical diagnosis.

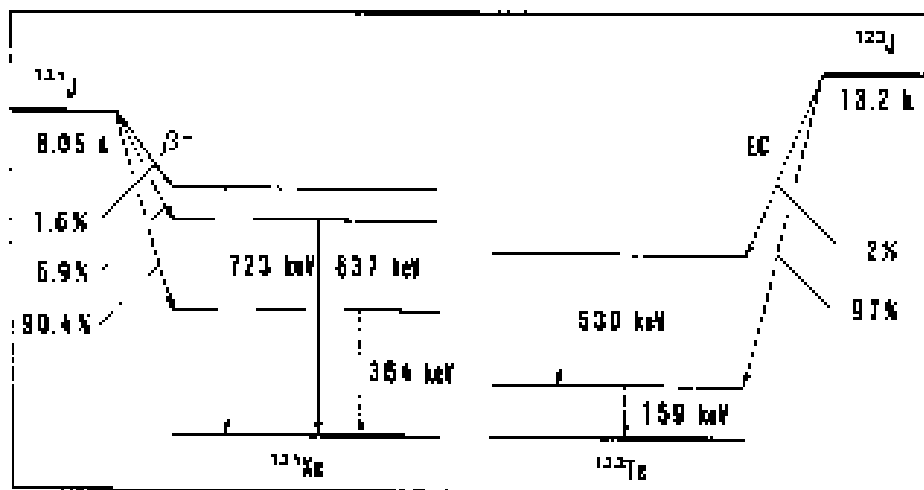


Fig. 2 Comparison of the physical properties between I-131 and I-123

The production of radioisotopes used in nuclear medicine can be made with solid, gaseous and liquid targets. Figure 3 is an example for a solid target for 30 MeV protons and a current of 200  $\mu$ A. The target material which is electrochemically plated on a solid copper backing is hit directly by the beam. The dissipated beam power of 6 kW can be removed by enforced cooling from the back-side of the target. To keep the power density low the beam strikes the target under an angle of 5°–7°. Thus the temperature on the target surface is kept below 150 °C.

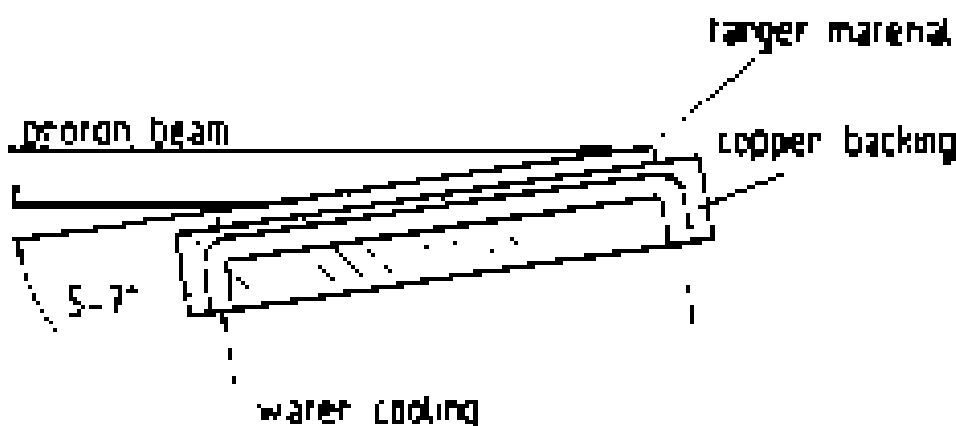


Fig. 3 Layout of a solid target

Figure 4 shows a target layout for gaseous or liquid target material. In contrary to the solid target the beam cannot hit the target material without entering the target vessel through a thin metal window. The target vessel itself has to be water-cooled as well to cool down the liquid or the gas.

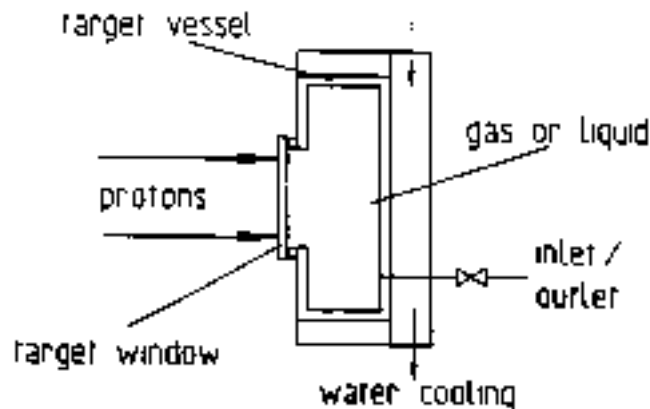


Fig. 4 Layout of liquid or gas target

## 2. TARGET BODIES AND WINDOWS

The choice of material for both the target body and window is dependent on the particular nuclide production process. Although a general rule does not exist, there are some aspects of the target bodies like activation, contamination, corrosion and cooling, which have to be considered [3, 4]. The parameters are influenced by the choice of bombarding particle, beam energy, beam current, material and solvent. The criteria for target-window materials should be the following:

- thickness of 1 – 200  $\mu\text{m}$
- pin-hole free
- high mechanical strength
- good thermal conductivity
- high melting point
- chemical resistance to oxidation

The target windows can be sealed either by O-ring or welding. This depends on the particular boundary conditions of cooling, temperature, pressure and radiation effects.

## 3. ACTIVITY CALCULATIONS

When irradiating a target material with charged particles from a cyclotron, the disintegration rate  $D$  of a produced radionuclide is:

$$D = IN\sigma(1 - e^{-\lambda t})$$

where

- $I$  = intensity of the irradiating particles (number of particles/cm<sup>2</sup> s)
- $N$  = number of target atoms
- $N = \frac{W \cdot K}{A_w} \cdot 6.02 \cdot 10^{23}$ .
- $W$  = weight of target material
- $K$  = natural abundance of target element
- $A_w$  = atomic weight
- $\sigma$  = formation cross section in barn ( $10^{-24}$  cm<sup>2</sup>)
- $\lambda$  = decay constant given by  $0.693/t_{1/2}$  (s<sup>-1</sup>)
- $t$  = duration of irradiation (sec)

$$1 \text{ Ci} = 3.7 \cdot 10^{10} \text{ disintegrations/sec}$$

From the equation it can be seen, that the amount of radioactivity produced, depends on the intensity and energy (cross section  $\sigma$  is related to energy) of the bombarding particles, the amount of target material, the half-life of the produced radionuclide and the duration of irradiation. The term  $(1 - e^{-\lambda t})$  reaches unity when  $t$  is approximately 4-5 half-lives of the radionuclide. At that time the yield of the produced nuclide becomes maximum. Production rates and decay become equal. Figure 5 shows this effect.

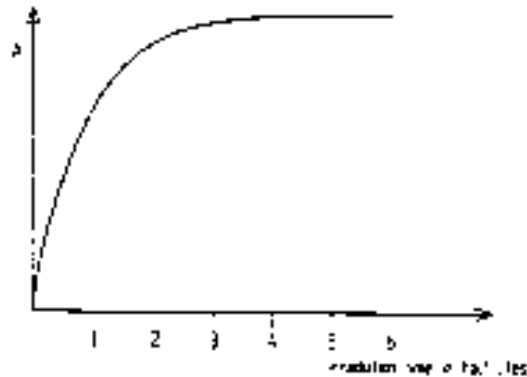


Fig. 5 Production of radionuclides. The activity reaches saturation in 4-5 half-lives.

#### 4. ACTIVITY TRANSFER

After irradiation the produced isotope is still in the target matrix (solid) or inside the target vessel (gas or liquid). In both cases the activity has to be transferred from the irradiation station into a hot cell for further processing. This transfer must be safe, reliable and sometimes fast and can be done either manually or automatically. For dose considerations and for safety reasons an automatic transfer is recommended. The commonly used transport systems are rabbit or conveyer devices (for solid targets) and pipelines (for liquids and gases).

#### 5. AUTOMATION

For routine (daily) production a microprocessor controlled system is absolutely necessary. Either a semiautomatic mode or a fully automatic mode guarantees a high reliability of the production process and a constant product quality. Moreover a remote handling of the target and the chemistry prevents personnel from obtaining a too-high radiation dose.

#### 6. MAIN RADIOISOTOPES

Table 1 summarizes the most important cyclotron-produced isotopes for medical applications. Common features for this radionuclide production are:

- production via (p,xn)-reaction
- proton energy ranges between 10 MeV and 30 MeV
- enriched isotopes for target material
- recovery of target material
- commercially available

**Table 1**

Most common cyclotron produced radioisotopes for medical diagnostics

Radioisotope	Half-life (h)	Nuclear reaction	Bombarding energy (MeV)
Gallium-67	78.3	Zn-68(p,2n)Ga-67	25
Bromine-77	57	Kr-78(p,2n)Rb-77 Rb-77 → Kr-77 → Br-77	30
Rubidium-81	4.6	Kr-82(p,2n)Rb-81	30
Indium-111	67.2	Cd-112(p,2n)In-111	22
Iodine-123	13.2	Xe-124(p,2n)Cs-123 Cs-123 → Xe-123 → I-123	30
Thallium-201	73.1	Tl-203(p,3n)Pb-201 Pb-201 → Tl-201	20
Fluorine-18	1.8	O-18(p,n)F-18	18

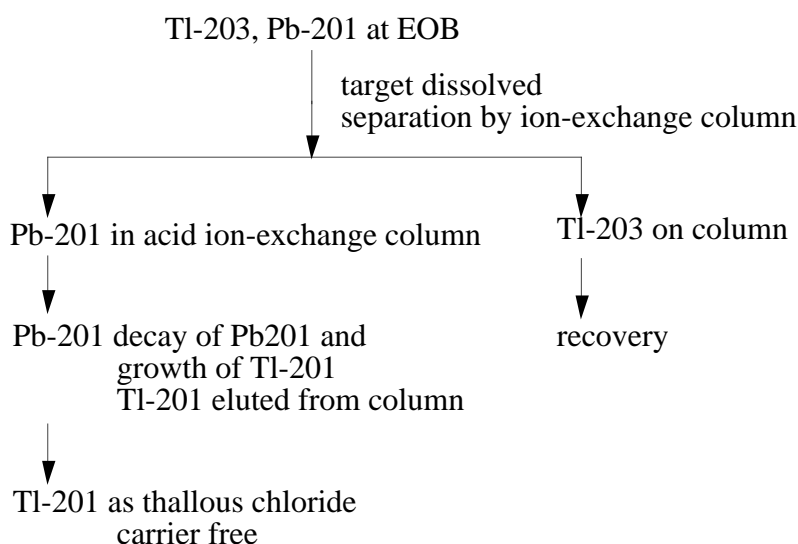
Methods of preparations for these cyclotron-produced radionuclides are described below.

### 6.1 Thallium-201

Half-life:	73.1 h
Nuclear reaction:	Tl-203(p,3n)Pb-201
Proton-energy:	29 MeV
Type of target:	solid target, Tl-203 electroplated on target backing
Target material:	Tl-203 > 90% enriched
Activity transfer:	rabbit or conveyer (irradiated target)
Separation:	chemical (Tl-203 from Pb-201; Pb-201 from Tl-201)

#### Production process

Immediately after the end of bombardment (EOB) the enriched Tl-203 is dissolved in acid and Pb-201 is isolated by the ion-exchanger method. The Tl-203 is retained on the column for the further recovery process. Pb-201 is then absorbed on another ion-exchange column and enough time is allowed for Pb-201 to decay to Tl-201. Tl-201 is then eluted as thallos chloride in carrier-free form.



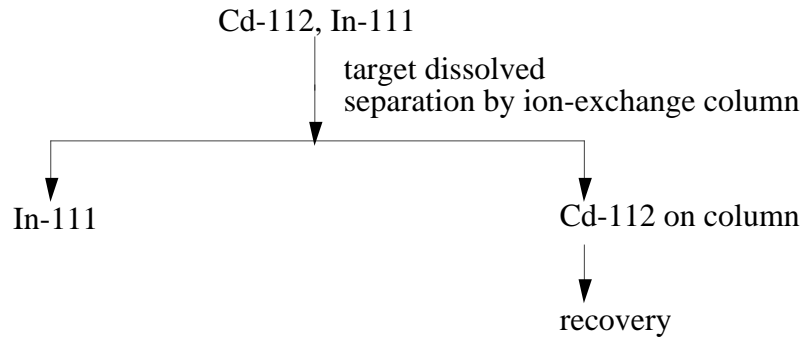
### 6.2 Indium-111

Half-life:	67.2 h
Nuclear reaction:	Cd-112(p,2n)In-111
Proton energy:	22 MeV
Type of target:	solid target, Cd-112 electroplated on target backing
Target material:	Cd-112 > 90% enriched

Activity transfer: rabbit or conveyer (irradiated target)  
 Separation: chemical (Cd-112 (extremely toxic) from In-111)

#### Production process

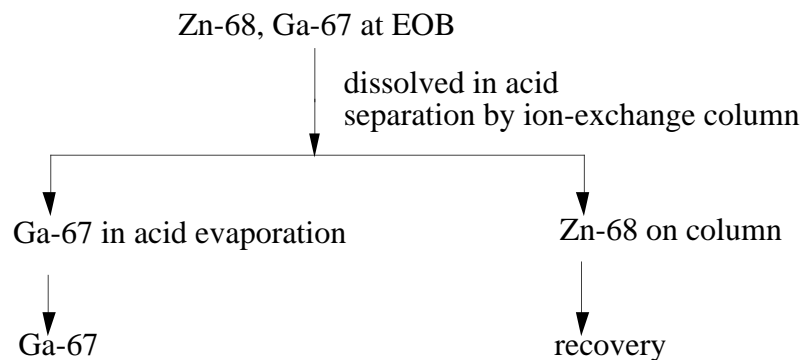
After irradiation the enriched Cd-112 target is dissolved in acid. The solution is passed through an ion-exchange resin. In-111 is removed by elution. Cd-112 stays on the column and is used for further recovery.



### 6.3 Gallium-67

Half-life: 78.3 h  
 Nuclear reaction:  $Zn-68(p,2n)Ga-67$   
 Proton energy: 25 MeV  
 Type of target: solid target, Zn-68 electroplated on target backing  
 Target material: Zn-68  $\geq$  98 % enriched  
 Activity transfer: rabbit or conveyer (irradiated target)  
 Separation: chemical (Zn-68 from Ga-67)  
 Production process

When the irradiation of the enriched Zn-68 target is finished the target is dissolved in acid. The solution passes an ion-exchange column, where Zn-68 is kept back on the resin while the Ga-67 passes through.

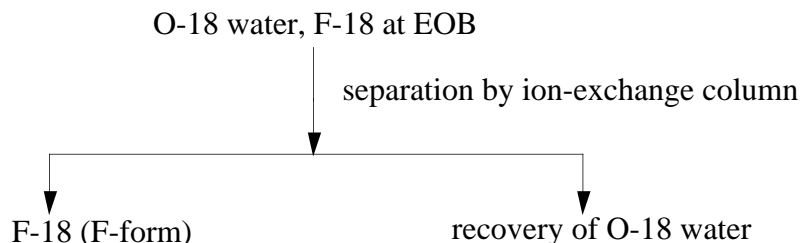


### 6.4 Fluorine-18

Half-life: 110 min  
 Nuclear reaction:  $O-18(p,n)F-18$   
 Proton energy: 18 MeV  
 Type of target: liquid (water target)  
 Target material: O-18 90 % enriched  
 Activity transfer: pipe line (F-18 in water)  
 Separation: chemical (fluorine from water)

## Production process

The F-18 produced during irradiation is dissolved in the target water. Separation of F-18 from water is done via ion exchange column.

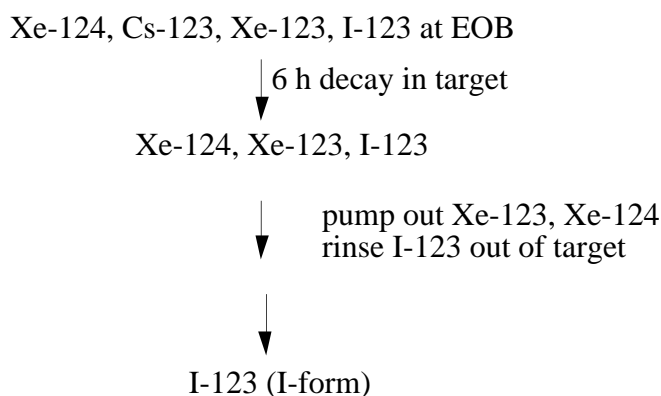


## 6.5 Iodine-123

Half-life:	13.2 h
Nuclear reaction:	$\text{Xe-124}(p,2n)\text{Cs-123} \rightarrow \text{Xe-123} \rightarrow \text{I-123}$
Proton energy:	30 MeV
Type of target:	high pressure gas target
Target material:	Xe-124 > 99.8 % enriched
Activity transfer:	pipeline (I-123 activity dissolved in water)
Separation:	physical (Xe-gas from solid I-123)

## Production process

For a period of 6 hours after the end of bombardment the Xe-123 is still kept in the target to allow Xe-123 to decay to I-123. In a next step the Xe gas is cryogenically pumped out of the target into a storage vessel for reuse. The I-123 is dissolved in water and rinsed out of the target.



## 7. ROUTINE PRODUCTION SYSTEMS

### 7.1 Ultra-Pure Iodine-123 production via KIPROS

An example for a gas target arrangement for routine production is the Karlsruhe Isotope Production System KIPROS (Fig. 6). This system provides ultra pure iodine-123 in large batch sizes (1 - 4 Ci in 6 h). Iodine-123 has begun to replace the reactor isotope iodine-131 (half-life: 8.05 days) used until now.

Iodine-123 has the following important advantages:

- lower radiation dose for the patient (a factor 60-100 less than for iodine-131)
- lower radiation dose for the hospital personnel,
- markedly better scintigraph quality and hence a higher diagnostic power,
- lower environmental contamination (a factor 5900 lower than for iodine-131).

Up to now, all the known iodine-123 production methods produce large amounts of undesirable by-products in the form of iodine-124 or iodine-125. Both these isotopes possess disadvantages comparable to those of iodine-131. With the aim to produce iodine-123 with as little impurity as possible, a new production method via the  $Xe-124(p,2n)Cs-123$  reaction was developed:

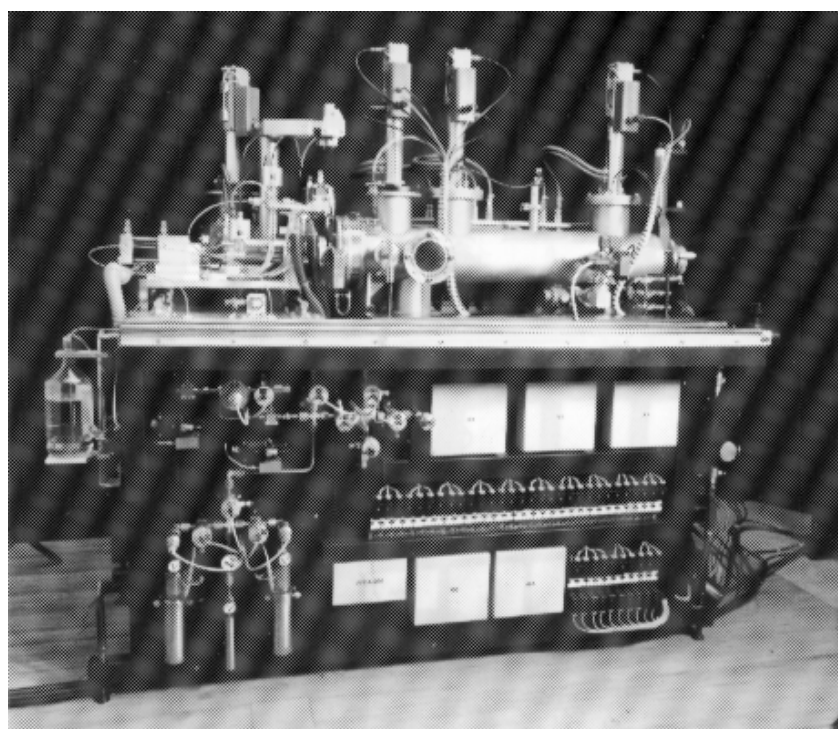
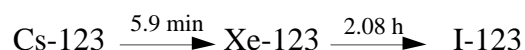


Fig. 6 High pressure gas target system KIPROS for the production of ultra-pure I-123. A sophisticated beam diagnostic system in front of the target assures a proper alignment of the beam. KIPROS is completely operated with a Simatic S-135 microprocessor system.

The production of the ultra-pure iodine-123 requires a very highly enriched Xe-124 gas as target material. In the procedure described here, Xe-124 with an enrichment  $> 99.8\%$  (natural abundance  $0.1\%$ ) is used, with the consequence that the end product iodine-123 has only a contamination for I-125 of  $4 \times 10^{-5}$  and I-124 of  $5 \times 10^{-7}$  at 24 h after EOB.

As the cost of a litre of enriched Xe-124 is very high it is important to keep the target volume as small as possible and at the same time be able to control the beam power,  $50 \mu A \times 30 \text{ MeV} = 1.5 \text{ kW}$ , generated during irradiation.

KIPROS consists of a high pressure gas target, a sophisticated diagnostic system for proper adjustment of the beam onto the target and a chemistry unit for the delivery of I-123 as iodide in  $0.02 \text{ N NaOH}$ . The target body is made out of nickel-plated aluminium to reduce activation and radiochemical contamination, and to assure proper cooling. The target is



operated at a pressure of 14 bars with beam currents up to 50 microamperes. The production yield for I-123 with 30 MeV protons is 10 mCi/Ah.

To prevent gas losses in case of target window ruptures a dedicated safety system is provided. It consists of a safety chamber in front of the target and a fast closing valve (12 ms closing time) about 8 m upstream in the beam line. The target window can be changed remotely with a robot (Fig. 7) so that a foil rupture during irradiation does not considerably influence the production schedule.

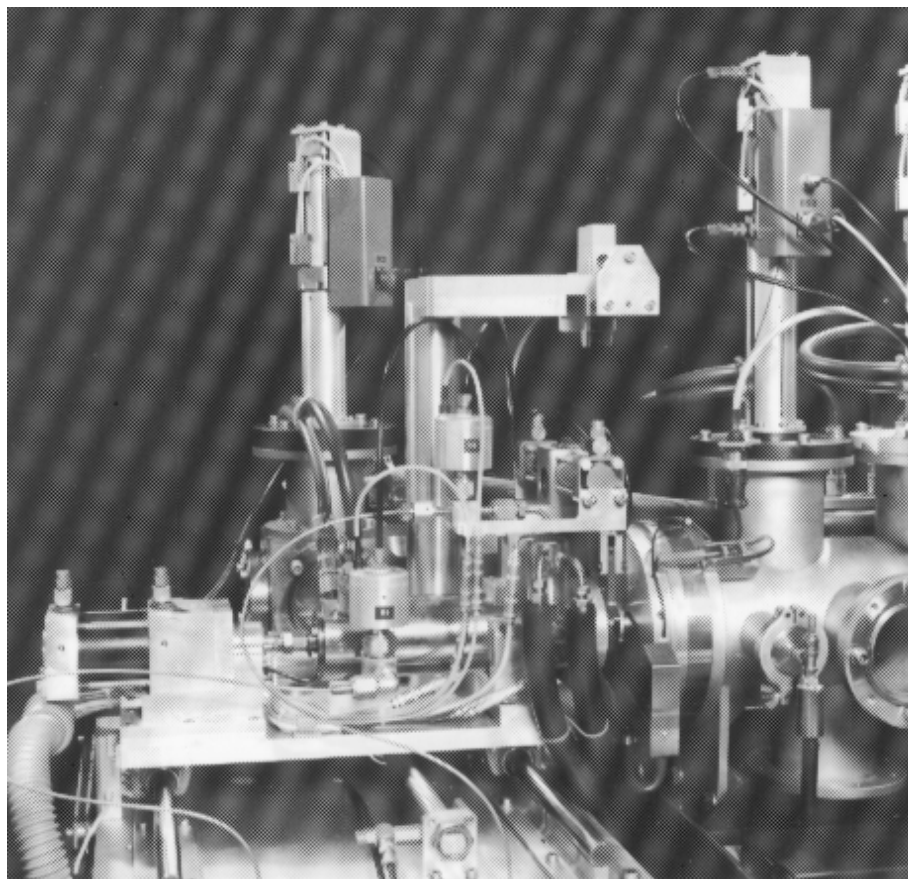


Fig. 7 Nickel-plated aluminium target with window flange in front. A robot changes automatically the target window in case of foil rupture. As part of the target volume there is a cold finger for cryogenic gas transfer from the storage vessel into the target (left side).

After an irradiation cycle the xenon gas is cryopumped out of the target and subsequently the iodine-123 deposited on the cooled walls is washed out by means of 40 ml of distilled water.

The essential advantages of the KIPROS method are:

- highest purity of iodine-123 produced
- high production efficiency (300 - 500 mCi/accelerator hour),
- low production costs by the operation of a relatively small accelerator facility and microprocessor-controlled production.

## 7.2 Chemistry and quality control

The hardware configuration of the chemistry unit for the production of I-123 is shown in Fig. 8 while the flow diagram which illustrates the function of the concentration process is

shown in Fig. 9. At the end of the target wash-out procedure the active solution is purged from the target into the glass vessel inside the hot cell. An additional vacuum vessel traps the small amounts of radioactive gas coming from the target. The active solution is pumped through the ion-exchanger column where Bio Rex 5 is used as the column resin with an absorption efficiency > 99%. After the loading procedure the I-123 is eluted with 0.02 N NaOH from the column into the glass vial. The flow direction through the column during the elution process is opposite to the loading direction.

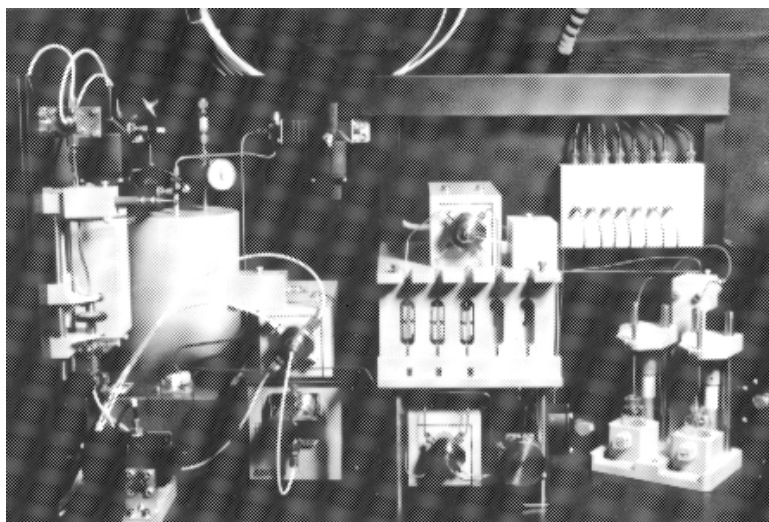


Fig. 8 Chemistry unit for the concentration of the iodine washout from 40 ml to 1.6 ml (0.02 N NaOH). An ion-exchanger with a special resin is used. The loading and reloading of the ion exchanger is carried out by HPLC pumps which allow precise control of the flowrates. In process measurement of the iodine activity is possible with small GM counters.

The chromatography pump keeps the flow rate constant, which can be preset before the loading or elution process starts. At the end of elution the main part of the activity (> 90%) is dissolved in a final process volume of < 1,6 ml of 0.02 N NaOH. The whole process from the beginning up to the point when the final product is inside the glass vial can be controlled either manually or fully automatically. Valves, pumps, cylinders, positions switches and sensors are connected to the processor (see Section 7.3). The activity is monitored with small GM sensors at a few positions to guarantee a reliable automatic process, which can be stopped in case of a system failure (for example: an accidental column breakthrough during the loading procedure).

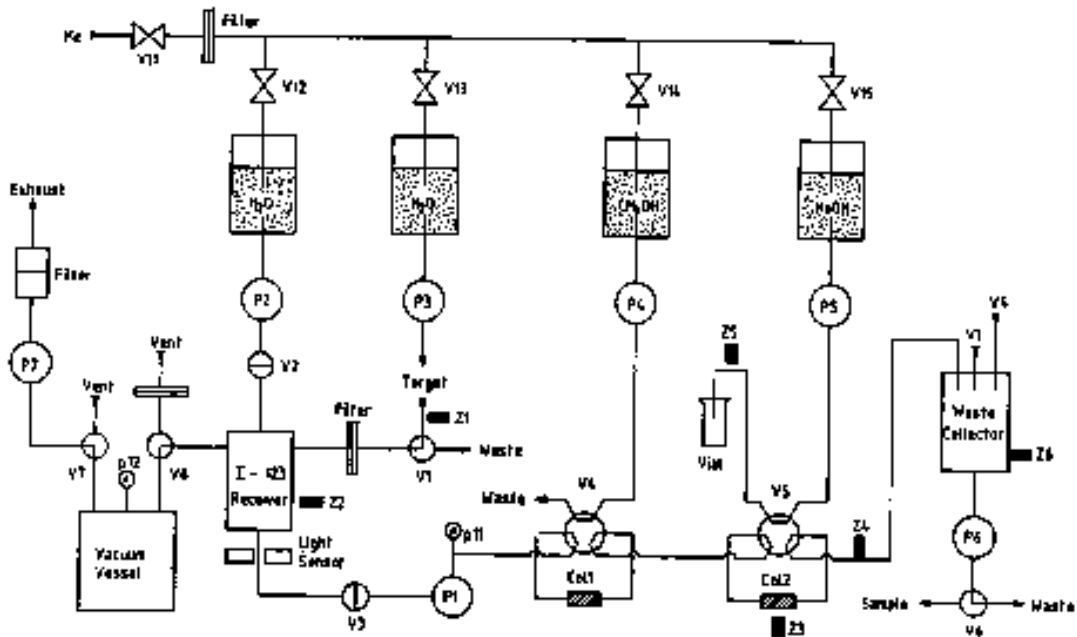


Fig. 9 Flow diagram of the I-123 concentration unit

The configuration of the multiport valves enables different samples to be obtained during the automatic run. The samples are used for the quality control.

The quality control includes tests for the product identity, the radionuclide purity, the radiochemical purity and the pyrogen concentration. The radionuclide purity is measured with a Ge detector while the radiochemical purity is determined by the thin-layer-chromatography method. The pyrogen concentration is checked with the Limulus-test.

### 7.3 Control system

The control system consists of the programmable controller type Simatic S5-135 U, the communication station with monitor and keyboard and the printer station (Fig. 10). The controller crate contains the following modules necessary for the operation of the production process:

- Central processing unit (CPU) with a 16-bit microprocessor, internal memories, data organisation and an external memory for the user software
- Communication processor 525 for the process documentation which enables the data transfer of all the various process parameters to a printer station
- Communication processor 526 for the communication between the controller and the terminal. Process commands can be entered via a keyboard, while status information (for example: position of valve) and system messages are displayed on the monitor Fig. 11
- Analog input modules for the measurement of analog process values
- Digital input modules for the connection of status indication signals
- Digital output modules for the connection of switching components.

The user software for the sequential and logical run of the process is written in a special language, called "STEP 5", which is optimized for the S5 Simatic controllers. The user software for the communication processors (CP 525 and CP 526) is written by entering values in the different masks which are created by the COM 525 and COM 526 system programs.

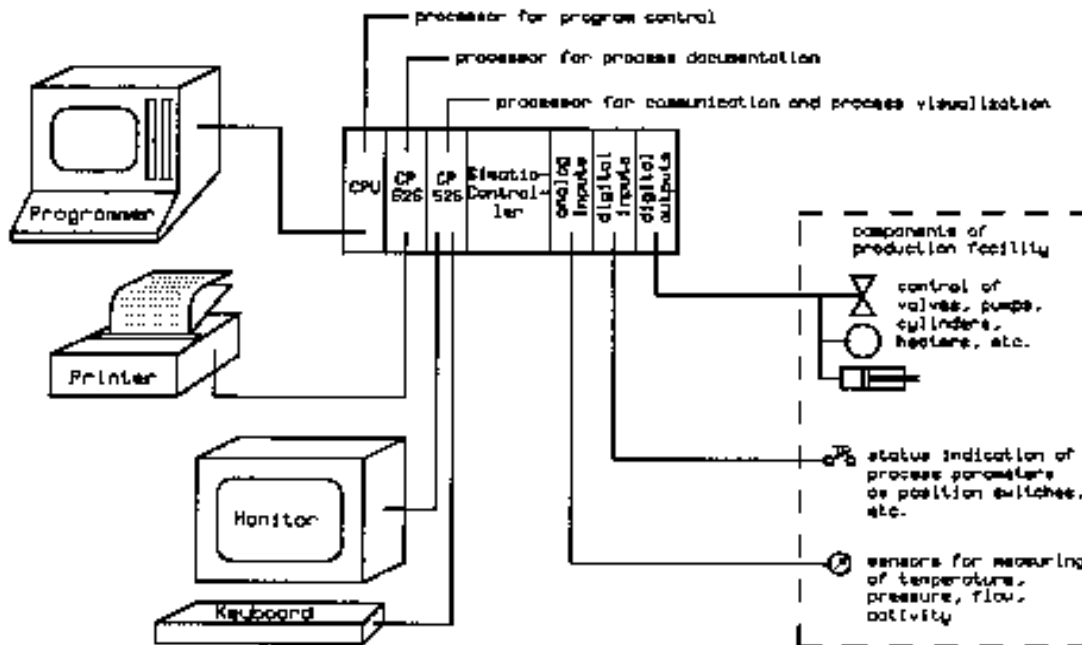


Fig. 10 Configuration of gas target control system

If RAMs are used as the external storage medium, the memory is buffered by a back-up battery in the central crate of the S5-135 U controller. The typical cycle time for the CPU is 3-100 ms, which depends on the user program volume. The edition and the transfer of the user program to the processor modules are performed with the programmer unit S5-PG 685 which can also be used for an on-line test of a running program. The status picture (Fig. 11) indicates the number of the current running program step, the start condition for the next step, a general description of what is carried out in each step, the activated components and the current value of a running timer. If the program is automatically stopped by an interlock, the reason is displayed in the lower part of the status picture, which is reserved for error messages and system information. At the end of the program the <Program End> information is displayed and the processor automatically switches back to the initial state. The processor allows a simultaneous run of two programs. The processor control enables the operation of the target system with a minimum of manpower and guarantees a reproducible production process and finally a reproducible quality of the final product.

#### 7.4 The Rb-81/Kr-81m generator system

The radionuclide Kr-81m (half-life: 13 s), which is the daughter of Rb-81 (half-life 4.65 h), has gained increasing importance for lung function diagnosis over the last years. The essential advantages of this radioisotope compared to the other radioisotopes used in this field today are:

- minimal radiation dose for the patient and hospital personnel,
- static and dynamic ventilation studies,
- no exhaust problems and also no risk of contamination.

The Kr-82 (p,2n) Rb-81 reaction is used for the production. During irradiation the Kr-82 gas (pressure: about 20 bars) is contained in a pressure vessel, which is sealed by a thin molybdenum-steel entrance window.

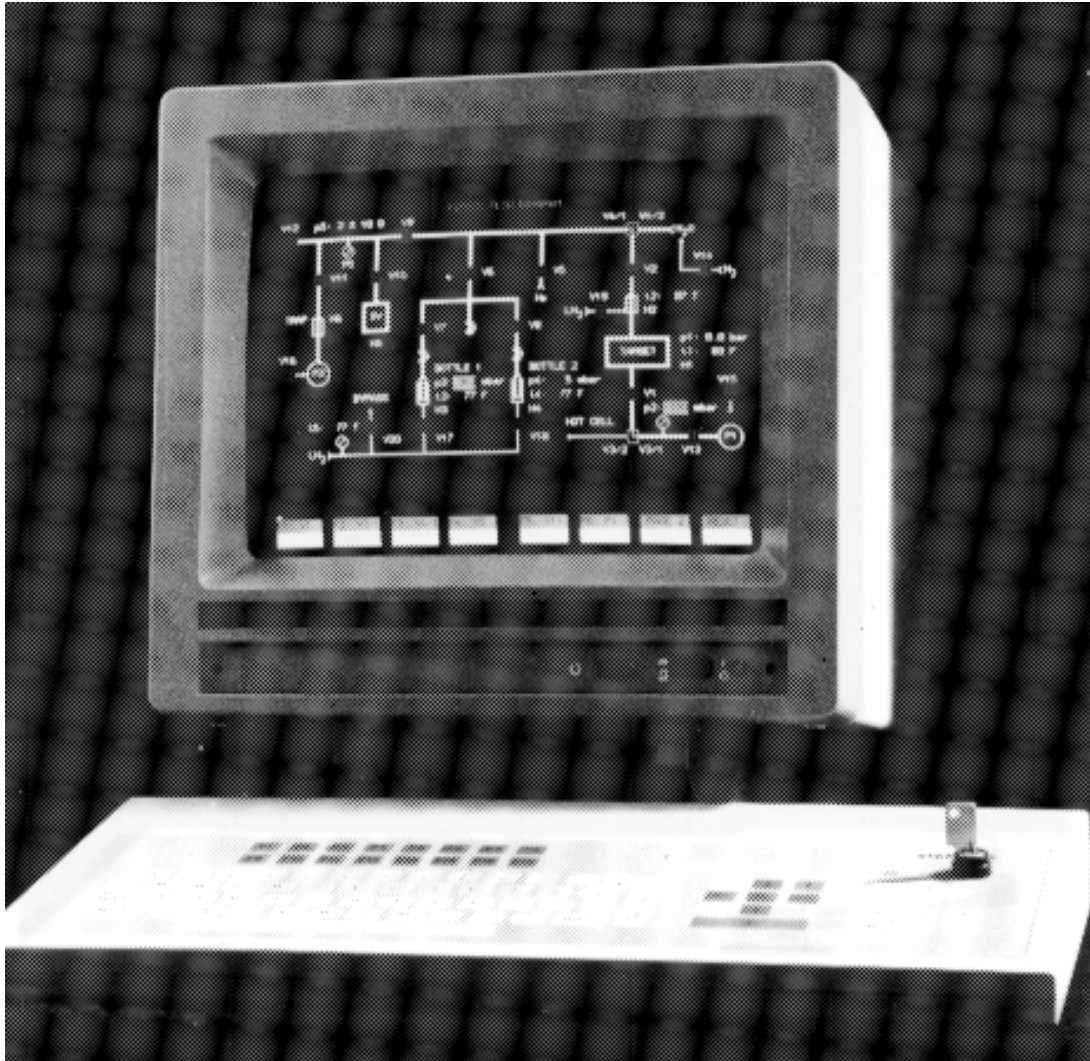


Fig. 11 Colour monitor with keyboard for the communication with the control processor

The target arrangement is similar to the Xe-target. The Rb-81 produced during irradiation, deposits on the cooled walls of the target vessel and is removed after the end of bombardment by means of sterile water. The Rb-81 is then pumped 15 m via a stainless steel pipeline to a hot cell located outside the irradiation room. There the Rb-81 dissolved in water is purged through a special ion exchanger which traps the Rb-81. This so-called generator is then fitted into a transportable lead shield and a complete quality test is carried out. The KfK possesses a pharmaceutical manufacturing permit for the Rb-81/Kr-81m generator according to paragraph 13 AMG. For the application of the generator in the hospitals it was imperative to develop a simple application system. The "Kryptovent II" system, (Fig. 12) which has been developed at KfK, is offered with the generators as a complete inhalation system.

The high pressure gas target system KIPROS is usable for highly-enriched target gases in particular, where it is necessary to minimize gas inventory and gas losses. This system is used for the production of ultra-pure I-123, Rb-81 and Br-77 at different production facilities in Europe, USA and Japan. The appropriate choice of nuclear reaction adapted to a compact cyclotron (maximum energy 30 MeV protons) combined with a sophisticated technique and a microprocessor controlled process, guarantees a reliable and cost-effective production of radioisotopes with high yields and constant product quality.



Fig. 12 Rubidium-81/Krypton-81 m generator and Kryptovent II for ventilation diagnostic

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