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STATUS REPORT ON RADIOISOTOPE PRODUCTION FOR BIOMEDICAL PURPOSES AT MILAN AVF CYCLOTRON

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Abstract. - The aim of this paper is to present a review of the most recent results obtained and the most likely developments in the field of radioisotope production for biomedical purposes. The work carried out includes the study of the excitation functions, radiochemical separations from irradiated matrices, radiochemical purity of the chemical forms suitable for use.

Introduction.- Since several years a research program of applied nuclear physics centered on radioisotope production for medical and for biological purposes has been carried out at the Milan AVF Cyclotron.

At present this program is carried out along these directions:

1) Radioisotope production with short half-life and low contamination characteristics for organ functional studies and medical diagnosis.
2) Radioisotope production with high specific activity for metabolic and toxicology studies on laboratory animals exposed to low doses of environmental pollutant metals.
3) Evaluation of trace elements in biologic matrices with proton activation analysis followed by selective radiochemical separation. This is particularly aimed at the evaluation of pollutant environmental elements for which the neutron activation analysis has severe sensitivity limits.

1. Radioisotopes for clinical uses.- Among the several radioisotopes studied, only a few proved of real interest to physicians. Therefore the largest efforts were concentrated on these in order to obtain the best results. These isotopes (^{123}I, ^{81m}Kr, ^{201}Tl, ^{195m}Au) are at present widely used in several investigations in clinical areas. For every radioisotope the study of excitation functions allowed to evaluate:

a) the need of employing an enriched target and the more suitable isotope for the enrichement.
b) the irradiation proton energy and the thickness of the target to minimize the contamination of other radionuclides.
c) the possible yields for the different irradiation conditions.
d) the irradiation set up and the cooling system required.

Particular separation techniques to recover the radioisotopes of interest from the bombarded matrices were developed. They are reported in Tables I-IV together with the yields obtained.

The radioisotopes with activities of the order of GBq, were used in clinical tests in the chemical forms reported in the tables.

TABLE I - ^{123}I Production

Dry distillation from ^{124}Te enriched target in oven at 500 °C under Helium gas carrier flux and NaOH trapping	
Mean production per irradiation	8 GBq
Irradiation time	5 hrs (1.5 μA)
Distillation efficiency	75%
Delivery form	NaI in NaOH
Contamination	1% (^{124}I)
Distillation time	1 hr
Clinical use	water content in pulmunary chest
Chemical form	^{123}I - antypirine

TABLE II - ^{81m}Kr Production

Washing with distilled water of gaseous Kr target, absorption of Rb radioisotopes on organic cation exchange resin	
Mean production per irradiation	3 GBq
Irradiation time	1.5 hrs (3 μA)
Recovery efficiency	95%
Delivery form	generator for gas elution
Contamination	0.001%
Time to charge the generator	1.5 hrs
Clinical use	Pulmunary ventilation
Chemical form	gas

TABLE III - ^{201}Tl Production

Pb radioisotopes separation from ^{203}Tl enriched matrix, followed by anion exchange separation of ^{201}Tl after 32 hrs growing up time (^{201}Pb decay)	
Mean production per irradiation	400 MBq
Irradiation time	3 hrs (3 μA)
Radiochemical treatment	3 + 2 hrs
Overall efficiency	95%
Delivery form	Tl (I) 98% in physiol. sol.
Contamination	0.3% ($^{200,202}Tl$)
Clinical use	Myocardial studies

TABLE IV - ^{195m}Au Generator studies

Dry distillation of Hg radioisotopes from thin gold targets, at 800 °C, mercury trapping on a quartz nitrogen cooled finger	
^{195m}Au yield	34 MBq/C
Separation time	2 hrs
Distillation efficiency	98%
^{195m}Au contamination expected	0.4% (^{197m}Au)
$^{195m,195}Hg \rightarrow {}^{195m}Au$ generator studies	in progress
Clinical use	Myocardial and cerebral studies

The production is not a routine one but is carried out in collaboration with a medical staff for research purposes, namely to set up new diagnostic procedures.

2. High specific activity radiotracers production for environmental studies.- Today daily intakes of trace elements by man are of the order of few micrograms or nanograms. Environmental toxicological studies thus require the use of extremely sensitive analytical techniques to determine very low amount of heavy metals in tissues and cellular components.

Environmental toxicological research on dose-response relationships of heavy metals requires experiments on laboratory animals exposed to "low doses" of trace elements which should reflect "present or actual environmental level" characteristics of polluted environment.

In these fields of research the use of radiotracers with very high specific radioactivity appears particularly advantageous but requires considerable care during their preparation and use.

The preparation of adequated amount of radiotracers was essentially carried out by (p,xn) reactions which produce carrier-free radioisotopes not readily available commercially.

As elsewhere the excitation function studies allowed to evaluate the best irradiation conditions to produce the radioisotopes in interest, although in this case the presence of radiocontaminants is not a large problem.

On the contrary, in the majority of the cases the presence of the matrix radioisotopes, produced via (p,pxn) reactions or following the decay of radioisotopes of interest, allows to evaluate the radiochemical separation efficiency.

Typical yields for some carrier-free radioisotopes produced by cyclotron irradiation are reported in fig. 1.

Radiotracers produced with cyclotron irradiation are theoretically carrier-free because all the atoms of the isotope produced are radioactive, arising from a parent which is different from the radiotracer produced.

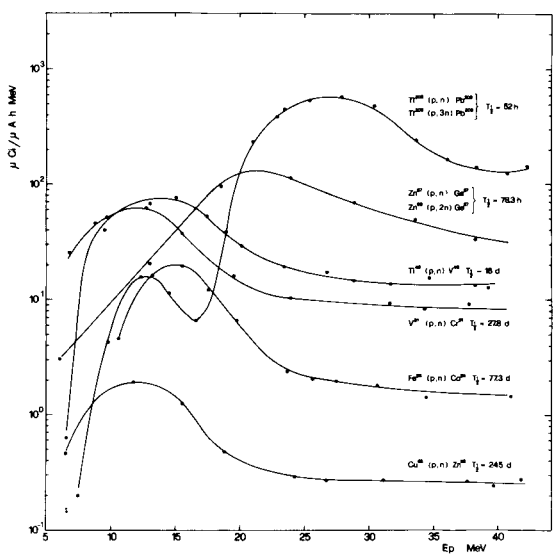

Fig. 1 - Excitation functions employed for the production of radionuclides for biological studies

The irradiated parent, however, may contain stable isotopes, of the radioisotope of interest, such as an impurity. More over, the weight of the irradiated target is normally of the order of hundreds of milligrams, the radiochemical separations generally include several steps, which are carried out using large columnes of reagents. The latter present a potential source for the introduction of carrier into the final radiotracer solution.

A determination of the total element concentration in the solution administred to laboratory animals was carried out with highly sensitive analytical methods as PAA, NAA and AAS analysis.

Values of the real specific radioactivity obtained are compared with theoretical values in Table V.

The same table also reports the radioactive concentrations in the solutions administred to laboratory animals in the biological studies carried out in the Ispra JRC Euratom Centre.

TABLE V - Radiotracers specific radioactivity

Radiotracer produced	Real specific act. (μCi/ng)	Theoret. spec. act. (μCi/ng)	Radioactive conc.(mCi/ml)
^{48}V	25	161	5
^{51}Cr	2	90.9	0.2
^{65}Zn	1.1	8.2	1
^{74}As	20	101	1
^{109}Cd	0.47	2.52	0.1
^{120}Sb	64.5	182	3
^{197}Hg	24	250	2
^{201}Tl	40	217	3
^{203}Pb	5.9	298	5
^{206}Bi	10	99.5	2

3. Proton activation analysis.- Within the research program on toxicology of heavy pollutant environmental metals, in collaboration with the Biology Division of JRC Euratom, Ispra, a method for the detection,at ppb levels, of trace elements in biological samples has been developed.

Trace elements in biological samples have been detected in the past with the NAA method. Unfortunately, NAA cannot be conveniently used for the determination of elements of great environmental importance like Pb, Tl, Ti, Ge, V etc. due to the low sensitivities of this method for these elements.

It turns out that for such elements the proton activation analysis (PAA) may be convenient. The method developed by us is therefore intended as complementary to NAA. As usual, the first step is the study of thin target excitation functions.

Due to the energy loss of charged particles into the various biological targets,the "thick-target" yields (MBq/C) must be calculated by integration of the "thin target" excitation functions for every different incident proton energy.

Biological samples, in tablet form (20 mm diameter, about 100-160 mg/cm^2 thick) pressed into an high purity graphite container are cased into a special freon cooled Faraday cup, and irradiated, in vacuum, with a proton beam current not higher than 0.5 μA to avoid burns or vaporizations.

After irradiation the samples may be analysed with customary γ spectroscopy methods to measure the induced radiactivity.

However the detection limit for every element is related to the background counts under the photopeak of the γ-emission considered for the element itself.

To reduce such background a radiochemical separation, selective for the various elements present in the biological samples is required.

The radiochemical selective separation was carried out with the dissolution/distillation apparatus following this schema:

- dissolution mixture: H_2SO_4/HNO_3
- oxidant: H_2O_2 30%
- distillation medium: HBr

This procedure separates the elements in three main groups.
- uncondensable elements (halogens)
- volatile elements as halogenides (Hg, As, Ge, Se, Te) or oxides (Os, Ru...) which are found in the distillate fraction
- non volatile elements (IA, IIA, first transition row metals, some heavy metals...) which are found in the sulphoric residue.

On the non volatile fraction the following radiochemical separations are performed:
- drying and redissolution with H_2SO_4 1M
- chromatography on TDO (tin dioxide, 30 - 50 mesh) column (Bi, Cr, Ga adsorbed)
- washing with H_2SO_4 1M
- chromatography on HAP (hydrated antimony pentoxide 30-50 mesh) column (Na, K, Pb... adsorbed).
- washing with H_2SO_4 1M (Be, Co, Mn, Ca, Sr... eluted).

Following this procedure the majority of background (radioactivity produced in biological base C, Na, O, Ca and so on) may be eliminated gaining in sensibility for every element in interest.

The residual background can so be considered as the natural one only.

In Table VI we report the detection limits for several elements present in trace in biological samples following a radiochemical proton activation analysis (RPAA).

A test carried out for lead content in certified NBS samples with PAA has shown a very good linearity (fig. 2) with a correlation factor r^2 greater than 0.999.

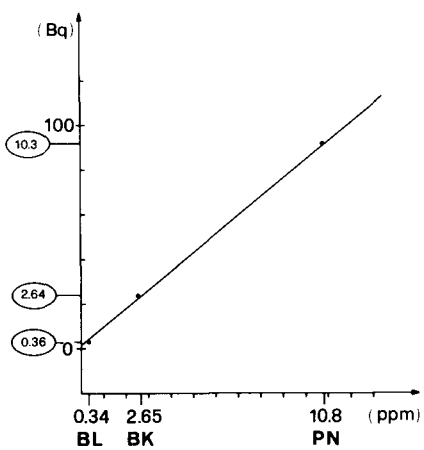

Fig.2 - Detected vs. certified Pb content in NBS samples.

The described procedure was employed to evaluate the lead content in pooled human serum and red blood cells of 15 unexposed subjects, obtaining the following results.
- RBC 109 ng/g total blood
- serum 4 ng/g total blood
- total blood 113 ng/g (wet tissue) = 12 µg/100 ml which is considered a tipical concentration for unexposed human blood.

The instrumental analysis of a sample of an exposed subject lead to 88 µg/100 ml for lead content in total blood.

TABLE VI - Calculated sensitivities in the hypothesis of an ambiental background only

Element	Employed nuclide	Sensitivities (ppm)
Pb	^{206}Bi	0.05
Cu	^{58}Co	1
Ti	^{48}V	0.06
Au	^{205}Hg	0.02
Zn	^{66}Ga	0.02
Tl	^{201}Pb	0.01
Ge	^{72}As	0.01
Hg	^{200}Tl	0.005

4. Summary.- The activities reported in this paper are likely to continue for the next two years at the Milan Cyclotron. Perhaps more emphasis will be placed on the development of generators if the interest warrants such an effort.

Within the next two years a new cyclotron, all particle, variable energy, MC-40, commissioned to Scanditronix, will be installed in the Milan area. The machine is funded by the Italian National Research Council (C.N.R.) as a dedicated tool for medical applications.

These and other research lines will be pursued, thereafter, with the new machine.

5. References.-

1. E. Acerbi et al. - ^{123}I Production at the Milan AVF Cyclotron - Journ. of Radioan. Chem. 34, 87 (1976)

2. E. Acerbi et al. - Nuclear Applied Physic at the Milan Cyclotron - Journ. Radioanal. Chem. 34, 191 (76)

3. E. Sabbioni et al. - Cyclotron Production of carrier free ^{48}V and preparation of different ^{48}V compound for metabolic studies in rats Radiochem. Radioanal. Letters 31(1), 39 (1977)

4. C. Birattari -Radioisotopes production by accelerators - Int. School of Rad. Damage and Protection Advances in Rad. Dosimetry and Prot. in Medicine Erice, sept. 79 - Plenum Press - N.Y. 269 (1980)

5. D. Basile et al. - Excitation Functions and Production of Arsenic Radioisotopes for Environmental Toxicology and Biomedical Purposes Int. Journ. of Applied Rad. and Isot. 31, 403 (1981)

6. E. Acerbi et al. - Kr(p,xn) excitation functions and ^{81}Rb - ^{81m}Kr generator studies Int. Journ. of Applied Rad. and Isot. 32, 465 (1981)

7. E. Sabbioni et al. - Environmental biochemistry of current environmental levels of heavy metals. The Science of the Total Environment 17, 257 (1981)