



INFN/TC-03/02
7 Febbraio 2003

**CYCLOTRON PRODUCTION OF “HIGH SPECIFIC ACTIVITY”
RADIOCHEMICAL FORMS OF VANADIUM, MANGANESE AND THALLIUM
FOR METALLO-TOXICOLOGICAL STUDIES**

Flavia Groppi¹, Claudio Birattari¹, Mauro Bonardi¹, Luigi Gini¹
Mario Gallorini³, Enrico Rizzio³, Enrico Sabbioni⁴, Enzo Menapace⁵
Dolores Arginelli⁶, Alberto Ghioni¹ and Hae Song Mainardi¹

¹*Radiochemistry Laboratory, Accelerators and Applied Superconductivity Laboratory,
L.A.S.A., via F.lli Cervi 201, I-20090 Segrate, Università degli Studi and National Institute of
Nuclear Physics, INFN Section of Milano, via G. Celoria, 16, I-20133 Milano, Italy*

³*Unit for Radiochemistry and Spectroscopy, CNR, via Taramelli 12, I-27100, Pavia, Italy*

⁴*Institute for Health and Consumer Protection, IHCP, JRC-Ispra, European Commission,
EC, via E. Fermi 1, I-21020 Ispra, Varese, Italy*

⁵*Division for Advanced Physical Technologies, ENEA,
via Don Fiammelli 2, I-40128 Bologna, Italy*

⁶*Institute for Radiation Protection, IRP, ENEA, I-13040 Saluggia, Vercelli, Italy*

Abstract

In this paper are presented the production methods for very “high specific activity” radionuclides (HSARNs) of vanadium (V), manganese (Mn) and thallium (Tl), which have been developed in our laboratories for labeling different chemical forms of these elements present in the echo-systems in ultra-trace amounts, for metallo-toxicological and bio-kinetic studies. Use was made of both *cyclotron* and thermal *nuclear reactor*. If the nuclear reaction and/or decay product has atomic number different from irradiated target, it is possible separating the radioactive nuclide from irradiated target, without *intentional* addition of isotopic carrier. These kinds of radionuclides are named No Carrier Added, NCA, and their *specific activity* is very high and can reach values close to the theoretical Carrier Free one, CF.

The experimental determination of specific activity, chemical and radiochemical purities is mandatory for all these kinds of applications.

PACS: 82.90.+j

*Published by SIS-Pubblicazioni
Laboratori Nazionali di Frascati*

1 INTRODUCTION

We showed in several previous papers how the use of “very high specific activity radiotracers” would be very effective for studying the behaviour of different chemical forms of chemical elements at ultra-trace level¹⁻³). In practice, the analysis of trace chemical species either inorganic or organo-metallic and the study of their effects on living organisms, require very sensitive analytical techniques. In most cases, the toxicological impact of Long Term and Low Level Exposure (LLE) to ultra-trace elements, is unknown and depends on both the *amount* of trace element and its *chemical form* in particular. These last points are the *key-factors* to set up experiments, which are representative of the real environmental behaviour of the chemical species under investigation^{1,3}).

In order to simulate the uptake of different chemical forms of ultra-trace elements, the use of short-lived and *High Specific Activity RadioNuclides* (HSARNs) offers an almost unique very accurate and representative method to carry out metallo-toxicological studies on both *cell cultures* and *laboratory animals*. It is evident that the direct and raw *extrapolation* to *humans* of results obtained is a difficult and questionable task, whereas the direct analysis of human tissues, body fluids and bioptic specimen offers only indirect information about the behaviour of chemical species in main body compartments.

The *activity* $\mathbf{A}(t)$ of a *radionuclide* (radioisotope has a less general meaning) in a radioactive preparation or substrate is measured in Bq in the *Systeme Internationale of units* SI, whereas its *activity concentration* $\mathbf{C}_A(t)$ is measured in either Bq kg⁻¹ or Bq m⁻³ of substrate itself. Conversely, the *specific activity* $\mathbf{A}_S(t)$ of the same radionuclide is *defined* as the ratio between the activity of a stated radionuclide and the mass \mathbf{m} (in kg) of *isotopic carrier* present in the sample, as by definition of Eq. (1):

$$\mathbf{A}_S(t) = \text{Activity of a RN on total mass of isotopic carrier} \equiv \mathbf{N}(t) \lambda \text{ m}^{-1} \quad (1)$$

in which: $\mathbf{N}(t)$ (atoms) is the number of radioactive atoms in the sample at time t (s), λ (s⁻¹) $\equiv \ln 2/t_{1/2}$ is the decay constant and $t_{1/2}$ (s) is the physical half-life of radionuclide itself. In the SI, this derived *quantity* is measured in Bq kg⁻¹, i.e. in most common cases in MBq μg^{-1} to GBq μg^{-1} .

With the term *isotopic carrier*, we mean the total amount of both stable and radioactive atoms of same Z (atomic number \equiv number of protons P of atomic nucleus) present in the sample⁴⁻⁸). Whenever it is experimentally proved that a radionuclide of atomic mass \mathbf{M} (kg mol⁻¹) is *absolutely free* of isotopic atoms (both stable and radioactive), the radionuclide concerned is defined *carrier-free CF*.

In this particular case only, its specific activity $\mathbf{A}_S(\text{CF})$ is a *physical constant*, an *intensive parameter* defined by the definition and identity (Eq. 2), i.e. \mathbf{N}_{Av} is the Avogadro's number in proper units. In practice, this condition is very rare and regards a few radio-elements only, i.e. super-actinoids and super-heavy elements produced in few atom amounts, radionuclides obtained by high-resolution mass separators and a few other selected cases⁶⁻⁹):

$$\mathbf{A}_S(\text{CF}) \equiv [\mathbf{N}_{Av} \mathbf{M}^{-1}] \lambda \quad (2)$$

A *molar specific activity*, or simply molar activity, $\mathbf{A}_m(t) \equiv M A_S(t)$ is also defined and is measured in Bq mol^{-1} , or in most cases $\text{GBq } \mu\text{mol}^{-1}$; in this case \mathbf{M} is the molar mass of labeled compound (kg mol^{-1}). Finally, a further useful parameter to specify the degree of isotopic dilution of a stated radionuclide, is the *isotopic dilution factor* $\mathbf{IDF}(t)$ which is a dimensionless quantity, defined by Eq. (3):

$$\mathbf{IDF}(t) = \text{mass of isotopic carrier on mass of RN} = \mathbf{IDF}^\circ \exp(\lambda t) \equiv A_S(\text{CF}) [A_S(t)]^{-1} \quad (3)$$

This dimensionless quantity $\mathbf{IDF}(t)$ changes with time t (s) after the End Of radiochemical Processing (**EOCP**) of irradiated target. In many practical cases, the radionuclide of interest is diluted in a substantial amount of stable atoms of same element and in the same chemical form⁶⁻⁹). Thus the $\mathbf{IDF}(t)$ increases with time with a very simple law, following the Eq. (3), where the quantity \mathbf{IDF}° represents the \mathbf{IDF} value at time zero, i.e. normally the EOCp.

In more complex cases, it is possible that the radionuclide of interest is mixed with other radioactive nuclides of the same element (isotopic impurities). In this last case the $\mathbf{IDF}(t)$ varies with time in a more complex way due to the different half-life of radionuclides concerned. In present paper we make the assumption that only one radionuclide of one element is present, that means having a radionuclidic purity of close to 100 %, while the *isotopic carrier* is constituted by stable atoms only.

In order to reach this kind of radioisotopic purity (same Z), it is necessary in almost all cases optimizing carefully the irradiation conditions in both cyclotron and nuclear reactor.

2 EXPERIMENTAL

In recent years, in order to produce HSARNs use was made of the Cyclotron of Joint Research Center of JRC-Ispra (Varese) of European Community, EC and the research Nuclear Reactor of the University of Pavia w/o National Research Council, CNR (Pavia, Italy).

In TAB. 1 are reported the nuclear reactions adopted, optimal energy range adopted and experimental values of \mathbf{IDF} at the EOCp, together the main side nuclear reaction concerned. For production of V, Mn and Tl radionuclides, targets of both natural and enriched isotopic composition have been used, the isotopic compositions are reported in TAB. 2.

All nuclear data were taken from Browne 1986¹⁰) and Firestone 1998¹¹). Some of our thin-target excitation function data, obtained in early times, are available in a recent IAEA compilation¹²). The statistical analysis of counting was performed in accordance with Smith¹³). Official IUPAC nomenclature and SI have been adopted^{14,15}).

As examples: nuclear reaction cross-sections are expressed in $\text{m}^2 \text{particle}^{-1}$ (i.e. $1 \text{ b} = 1 \text{ barn} = 10^{-28} \text{ m}^2$)¹⁵), while the production yield is given in MBq C^{-1} (i.e. $1.0 \text{ MBq C}^{-1} \equiv 3.6/37 \mu\text{Ci } \mu\text{A}^{-1} \text{ h}^{-1}$, where $1 \text{ Ci} \equiv 3.7 \cdot 10^{10} \text{ Bq}$)¹⁵). Nevertheless, to express both volumes and concentrations¹⁵), use was made of mL (millilitre) $\equiv 1 \text{ cm}^3$.

Finally, in present paper the following terminology was adopted⁵⁻⁷): **NCA** for No Carrier Added, **CA** for Carrier Added, **CF** for Carrier Free and **NCF** for Nearly Carrier.

TAB. 1: Nuclear reaction used for production of V, Mn and Tl HSARNs in No Carrier Added, NCA form, at Milano and Ispra Cyclotron Laboratories and at TRIGA MARK II thermal research Reactor of Pavia. In the Table are reported optimal energy range (MeV), calculated theoretical $A_S(\text{CF})$ (see text), experimental IDF° (see text), half-life of radionuclide produced^{10,11)} and main side reactions.

target nuclide	nuclear reaction	produced radionuclide	$t_{1/2}$	E- γ (keV)	energy range (MeV)	$A_S(\text{CF})$ (GBq g ⁻¹)	IDF°
²⁷ Al	(p,X)	²⁴ Na	14.959 h	1368.6	45-15	323.0	nd
²⁷ Al	(p, α d)	²² Na	2.6019 a	1274.5	45-15	0.23	nd
⁴⁵ Sc	(p,n)	⁴⁵ Ti	184.8 min	511@	15-9	836.6	nd
⁴⁵ Sc	(α ,n)	⁴⁸ V	15.9735 d	983.5	23-11	6.3	170
natTi	(p,n)	⁴⁸ V	15.9735 d	983.5	26-9	6.3	7-60
natCr	(d,xn)	^{52g} Mn	5.591 d	744.2	19#-9	16.6	nd
natCr	(p,xn)	^{52g} Mn	5.591 d	744.2	21-7	16.6	3200
natCr	(p,xn)	⁵¹ Mn \rightarrow	46.2 min	511@		2953	nd
natCr	(p,pxn)	⁵¹ Cr	27.702 d	320.1		3.4	CA
⁵⁵ Mn	(n, γ)	⁵⁶ Mn	2.5785 h	846.8	$\Phi = 9 \cdot 10^{16}$	803.0	$6 \cdot 10^5$
⁵⁹ Co	(p, α d)	⁵⁴ Mn	312.3 d	834.5	45-25	0.29	nd
¹²⁴ Te	(p,2n)	¹²³ I	13.27 h	158.97	28-17	71.0	NCF
natHg	(p,xn)	²⁰¹ Tl ²⁰² Tl	72.912 h 12.23 d	167.4 439.5	25-15 36-20	7.91 2.0	5 10
²⁰² Hg	(p,2n)	²⁰¹ Tl	72.912 h	167.4	19-13	7.91	5
natTl	(p,xn)	²⁰¹ Pb \downarrow ²⁰¹ Tl	9.33 h 72.912 h	331.2 167.4	27-19 27-19	61.8 7.91	100 10
²⁰³ Tl	(p,3n)	²⁰¹ Pb \downarrow ²⁰¹ Tl	9.33 h 73.1 h	331.2 167.4	27-19 27-19	61.8 7.91	100 10
natTl	(p,xn)	²⁰³ Pb	51.873 h	279.2	35-20	11.0	120

@positron annihilation radiation. # maximum energy available.

Φ = neutron flux density (n m⁻² s⁻¹). nd = non determined.

nat = target of natural isotopic composition (see TAB. 2).

TAB. 2: Isotopic composition of both natural and enriched targets used in present study for production of high A_S NCA radionuclides of vanadium, manganese and thallium^{10,11}).

Target nuclide	%	%	%	%	%	%	%	%
naturalTi	⁴⁶ Ti 8.0	⁴⁷ Ti 7.3	⁴⁸ Ti 73.8	⁴⁹ Ti 5.5	⁵⁰ Ti 5.4			
naturalSc	⁴⁵ Sc 100.00	mono-isotopic						
naturalCr	⁵⁰ Cr 4.345	⁵² Cr 83.789	⁵³ Cr 9.501	⁵⁴ Cr 2.365				
naturalTe	¹²⁰ Te 0.096	¹²² Te 2.603	¹²³ Te 0.908	¹²⁴ Te 4.816	¹²⁵ Te 7.139	¹²⁶ Te 18.95	¹²⁸ Te 31.69	¹³⁰ Te 33.80
enrichedTe	¹²⁰ Te ≈ 0	¹²² Te 0.9	¹²³ Te 0.11	¹²⁴ Te 91.86	¹²⁵ Te 3.17	¹²⁶ Te 1.81	¹²⁸ Te 1.55	¹³⁰ Te 1.01
naturalHg	¹⁹⁶ Hg 0.15	¹⁹⁸ Hg 9.97	¹⁹⁹ Hg 16.87	²⁰⁰ Hg 23.10	²⁰¹ Hg 13.18	²⁰² Hg 29.86	²⁰⁴ Hg 6.87	
enrichedHg	¹⁹⁶ Hg ≈ 0	¹⁹⁸ Hg ≈ 0	¹⁹⁹ Hg ≈ 0	²⁰⁰ Hg 0.1	²⁰¹ Hg 1.3	²⁰² Hg 98.6	²⁰⁴ Hg ≈ 0	
naturalTl	²⁰³ Tl 29.524	²⁰⁵ Tl 70.476						
enrichedTl	²⁰³ Tl 81	²⁰⁵ Tl 19						

In this paper we present the methods developed in our laboratories for production and uses of HSARNs of vanadium (⁴⁸V), manganese (^{52g}Mn, ⁵⁴Mn and ⁵⁶Mn) and thallium (²⁰¹Tl and ²⁰²Tl) in different oxidation states and chemical forms of toxicological and environmental relevance, for metallo-toxicological investigations envisaged.

Several experiments were carried out with multiple labelling techniques by simultaneous use of different HSARNs of same element in either different oxidation states or organo-metallic compounds, like: [^{52g}Mn]Mn(II), [⁵⁴Mn]Mn(VII), [⁵⁶Mn]Mn(II) and [²⁰¹Tl]Tl(I), [²⁰²Tl]Tl(III), dimethyl[²⁰²Tl]thallium(III) cation. Moreover several inorganic and coordination compounds of vanadium have been labelled with very high specific activity NCA ⁴⁸V (TAB. 3).

Some of these labelled compounds are reported in TAB. 3. All biological experiments on both cell cultures and laboratory animals were carried out in collaboration with JRC-Ispra (Varese) of European Commission, EC.

TAB. 3: Chemical species labelled with very high specific activity ^{48}V , $^{52\text{g},54,56}\text{Mn}$ and $^{201,202}\text{Tl}$ very high specific activity No Carrier Added, NCA, radiotracers.

radionuclide	oxidation state	chemical form	IUPAC nomenclature ¹⁴⁾
^{48}V	III	$[\text{}^{48}\text{V}]\text{V}^{3+}$	vanadium(III) cation
^{48}V	IV	$[\text{}^{48}\text{V}]\text{VO}^{2+}$	oxovanadium(IV) cation
^{48}V	IV	$[\text{}^{48}\text{V}]\text{porphyrin}$	vanado(IV)porphyrin
^{48}V	V	$[\text{}^{48}\text{V}]\text{VO}_2^+$	dioxovanadium(V) cation
^{48}V	V	$[\text{}^{48}\text{V}]\text{VO}_3^-$	trioxovanadate(V) anion
^{48}V	V	$[\text{}^{48}\text{V}]\text{VO}_4^{3-}$	tetraoxovanadate(V) anion
^{48}V	V	$[\text{}^{48}\text{V}]\text{VS}_4^{3-}$	tetrathiovanadate(V) anion
$^{52\text{g}}\text{Mn}$	II	$[\text{}^{52\text{g}}\text{Mn}]\text{Mn}^{2+}$	manganese(II) cation
^{54}Mn	II	$[\text{}^{54}\text{Mn}]\text{MnO}_4^-$	tetraoxomanganate(VII) anion
^{56}Mn	VII	$[\text{}^{56}\text{Mn}]\text{Mn}^{2+}$	manganese(II) cation
^{201}Tl	I	$[\text{}^{201}\text{Tl}]\text{Tl}^+$	thallium(I) cation
^{202}Tl	III	$[\text{}^{202}\text{Tl}]\text{TlCl}_4^-$	tetrachlorothallate(III) anion
^{202}Tl	III	$[\text{}^{202}\text{Tl}]\text{TlCl}_6^{3-}$	hexachlorothallate(III) anion
^{202}Tl	III	$[[\text{}^{202}\text{Tl}]\text{Tl}(\text{CH}_3)_2]^+$	dimethylthallium cation
^{202}Tl	III	$[\text{}^{202}\text{Tl}]\text{Tl}(\text{CH}_3)_3$	trimethylthallium

2.1 Reagents and chemical equipment

Ultra-high purity water of Type I (ASTM and ISO 3696) was produced with a Millipore (USA) Milli-RO/Milli-Q equipment supplied with deionised water obtained from a mixed-bed twin ion-exchange column. A total oxidable carbon, TOC, value of 10 ppb was achieved. All equipment was made by Teflon-PFA (Nalgene, Nalge Co., UK), for operations at temperature up to 220 °C. At higher temperatures use was made of quartz-ware of nuclear grade (Supra-Sil). All the acids and organic chemicals (organic solvent, chelants) were analysed for metal impurities by graphite-furnace atomic absorption spectrometry, ET-AAS (LASA), inductively coupled plasma optical-emission spectrometry, ICP-ES (JRC-Ispra) and instrumental neutron activation analysis, INAA, by high-resolution gamma spectrometry (Pavia). Concentrated metal standard solutions (Sigma-Aldrich, BDH) were diluted as required for the standard additions and for method evaluation, by both ET-AAS, ICP-ES and INAA. Ultra-high purity metal targets were purchased from Goodfellow Metal (UK), J&M (UK) and Aldrich Chimica (Italy). All ion exchange resins used (AG1x8, AG50Wx8, Chelex100, 100-200 mesh, others) were of analytical grade purity (Bio-Rad, UK). Suitable portions of resins were

preconditioned by swelling in either high purity water, buffer or acidic solution and then filled into polypropylene columns (Bio-Rad Econo-columns, UK) and repeatedly washed, up to reach a constant pH value of the eluate.

2.2 Instrumentation

2.2.1 Nuclear activation runs were performed at the *compact cyclotron* of JRC-Ispra of EC (Scanditronix MC40, Sweden) and at the TRIGA MARK II (General Atomics, USA) *thermal nuclear reactor* of University and CNR Pavia. The accelerator ($K=38$) gains proton and alpha beams, with energy variable up to 38 MeV, as well as deuterons with energy up to 19 MeV. The nuclear reactor is a conventional 250 kW research reactor, with 30 % enriched ^{235}U fuel rods. A thermal nuclear flux density varying from 10^{16} to $9 \cdot 10^{16} \text{ n m}^{-2} \text{ s}^{-1}$ was used in different cases (INAA and isotope production)¹⁶. The epithermal component of neutron spectrum was experimentally measured by cadmium shielding and was less than 10 %.

2.2.2 High-resolution gamma spectrometry was performed, by using four (50 cm^3) high-purity coaxial germanium HPGe detectors. The intrinsic efficiency was 15 % (EG&G ORTEC, USA), with a peak to Compton ratio of 30 to 1 at 1332.50 keV, FWHM 2.3 keV (^{60}Co point source). All detectors were connected with spectroscopy amplifiers (EG&G, mod. 572, 672) and A/D 2x4096 multi-channel analysers, MCAs (EG&G ORTEC, USA, mod. 918A, 919). The spectroscopy amplifiers were set to gain a channel/energy conversion factor 2 to 1. Gamma spectra in the energy range up to 2000 keV were acquired and analysed by Gamma Vision 5.2 for Windows s/w package (EG&G ORTEC, USA, mod. A66-B32). The efficiency data, obtained by decay corrected certified point source of ^{152}Eu , 41.1 kBq (overall uncertainty 2 %) (CIS, CEA, France), have been fitted by both Gamma Vision and S/W package TableCurve 1.10 for Windows (Jandel Scientific, AISN Software, Germany)¹⁷⁻¹⁹.

2.2.3 Beta spectrometry by liquid scintillation counting, LSC, was performed by a 1000 channel Liquid Scintillation Counter (Beckman, USA, mod. LS5000TD), with: three energy window capability, random coincidence monitor (RCM) and Horrocks Number ($H^\#$) quenching correction method. The quenching correction curves were experimentally determined by addition of increasing amount on CH_3NO_2 and CCl_4 to scintillation cocktails for aqueous solutions of high ionic strength Ultima-Gold, Ionic-Fluor and Pico-Aqua (Canberra-Packard, USA)^{19,20}.

2.2.4 Metal determinations were performed in order to verify chemical purity of labelled compounds, as well as determining experimental specific activity in No Carrier Added form, with ET-AAS (Varian, USA, mod. SpectrAA30, LASA), ICP-ES (Perkin Elmer mod. 5500, USA, JRC-Ispra), for most elements (ex: Pb, Tl, Cd, Ti, V, Cr, Fe, Pd, Zn, Cu, etc.). Moreover, for some particular metal (i.e: Os, Au, Ir, Ru, Sc, Sn) we used INAA, (TRIGA Mark II nuclear reactor Pavia), even if this technique could determine at least 35 trace elements simultaneously¹⁶. Some trace metal determinations (As, Se, Sb, Cu, Zn, Ga)

were performed by anodic and cathodic stripping voltammetry (ASV, CSV) too. We used a polarograph/voltamperimeter, with hanging Hg dropping electrode, HMDE (Metrohm Heriseau, Switzerland, mod. Polarecord E506, E608, 648). For many elements an inter-comparison between the different analytical techniques was carried out²¹⁻²⁶.

3 RESULTS AND DISCUSSION

3.1.1 High specific activity ⁴⁸V radiotracer production by ^{nat}Ti(p,xn) nuclear reactions:

Titanium of natural isotopic composition (TAB. 2) is suitable for production of high-purity ⁴⁸V ($t_{1/2} = 15.9735$ d)^{10,11} by (p,xn) nuclear reactions, due to the fact that all the other neutron-poor radionuclides of V are either very short-lived (from ⁴³V to ⁴⁷V) or long-lived like ⁴⁹V ($t_{1/2} = 330$ d). Moreover this last radionuclide that is produced with low yield due to its long half-life and isotopic target composition, decays by EC and does not present any γ emission, being undetectable by γ -spectrometry^{10,11,17,18}. In fact, due to the isotopic composition of ^{nat}Ti, the nuclear reaction to optimise the ⁴⁸Ti(p,n), is in the lower proton energy region available (21 to 7 MeV). In this energy range a thick-target yield of 6.2 GBq C⁻¹ (600 μ Ci μ A⁻¹ h⁻¹) is achieved. High purity (4N5) metal Ti sheets of natural isotopic composition, 1.1 mm thick (i.e 500 mg cm⁻²) and 10 mm in diameter were enclosed in ultra-high purity (9N) Al foils, 16 and 10 μ m thick (Goodfellow Metals, UK), in order to avoid possible cross-contaminations from cyclotron beam line.

After irradiation, the Ti targets were leached with diluted HNO₃ in order to decontaminate the Ti metal from ²⁴Na and ²²Na that are produced by activation and recoil from Al envelope, via (p,X) nuclear reaction (see TAB. 1). The presence of ²⁴Na must be avoided due to the very high energy of its gamma rays at 2754 and 1369 keV^{10,11}. In particular, these high-energy gammas could induce formation of single and double escape peaks in HPGe semiconductor detectors. ²²Na is produced with very low yield compared to ²⁴Na, nevertheless due to its very long half-life its presence is undesirable in metal-toxicological experiments. After a short irradiation of 4 hours, with a 10 μ A beam current 0.9 GBq (24 mCi) of ⁴⁸V are obtained in the target at the End Of Bombardment, EOB.

Proton irradiation on Ti targets leads also to production of several Sc radionuclides by side (p, α xn) nuclear reactions: ⁴⁸Sc ($t_{1/2} = 83.82$ d) and ⁴⁷Sc ($t_{1/2} = 3.35$ d) in particular^{10,11}.

Summary of main features of vanadium chemistry in aqueous media

Vanadium(V) does exist as either mono-nuclear trivanadate(V), VO₃⁻ (metavanadate) or tetravanadate(V), VO₄³⁻ and other iso-polynuclear anionic species (polyvanadates) like V_nO_{3n}ⁿ⁻, [V_nO_{3n}(OH)]³⁻, [VO_n(OH)_m(H₂O)]²⁻, which are present primarily in basic solution with stability decreasing with pH reduction^{29,30}. Under reducing conditions V(III) and V(II) species are also known^{29,30}.

We avoided this complex situation operating in mild oxidising acidic solution. The earlier radiochemical procedure that was developed for separation of NCA ⁴⁸V from both irradiated Ti target and Sc radionuclides was long and time consuming. It was based on a double chromatographic separation on anion exchange resin (Bio-Rad AG1x8, 100-200

mesh). Use was made of HF and mixtures of HCl and oxalic acids (H₂ox) of different concentrations as eluting agents. The method was based on the different behaviour of V(V) in acidic medium, as dioxovanadium(V) cation, VO₂⁺ and V(IV), as either oxovanadium(IV), VO²⁺ (vanadyl cation) or oxovanadium(IV) aquacation, [VO(H₂O)₅]²⁺ (aquavanadyl cation). The formation of a strong anionic complex of V(IV) with oxalic acid *cis*-[VO(ox)₂]²⁻ in 0.1 M HCl / 0.1 M oxalic acid mixture is also concerned with the separation. This complex is decomposed and converted to [VO(H₂O)₅]²⁺ aquacation increasing the concentration of HCl as eluent (0.4 M), without changing of V oxidation state (IV) that is the much more stable in acidic condition^{27,28}).

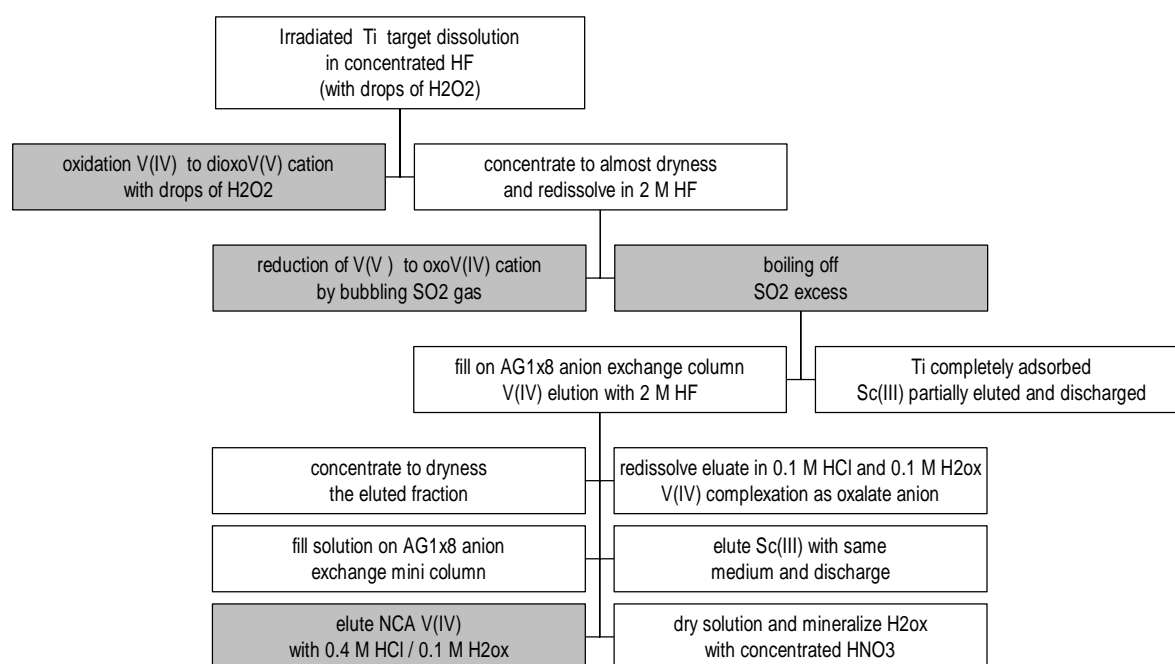


FIG. 1: Simplified scheme of earlier radiochemical separation of ⁴⁸V from irradiated Ti target and Sc radioactive by-products.

The oxidation state of vanadium was tested - in a higher concentration range - by using EPR spectrometry, due to the fact that V(V) is diamagnetic (d⁰ configuration), while V(IV) is paramagnetic (d¹ configuration)^{27,28}. The overall radiochemical yield referred to ⁴⁸V was 85 %. No Sc radionuclides were detected in the ⁴⁸V final fraction by HPGe γ -spectrometry. The decontamination factor from irradiated Ti target was of the order of 5 $\cdot 10^5$ (i.e. 100 ng in total in 5 mL of final solution), measured by ICP-ES spectrometry.

The A_S of the tracer at the EOCP was determined by INAA, via ⁵¹V(n, γ)⁵²V nuclear reaction^{10,11}) and was larger than 900 MBq μg^{-1} . The complete mineralization of final solution from oxalic acid was verified by liquid scintillation counting, by spiking the solution with ¹⁴C labelled [¹⁴C](COOH)₂. FIG. 1 shows the simplified scheme of Ti/V/Sc radiochemical separation described above.

3.1.2 High specific activity ^{48}V radiotracer production by $^{45}\text{Sc}(\alpha, n)$ nuclear reaction

In order to improve both speed and yield of radiochemical separation for preparation of very high A_S ^{48}V , a completely different nuclear route was chosen, based on α particle induced nuclear reactions on ^{45}Sc target, i.e. that is mono-isotopic (TAB. 2). The irradiations were carried out at α particle energy of 23 MeV, on an high purity (4N) metal Sc target, 0.2 mm thick (Alfa Chemicals, Italy).

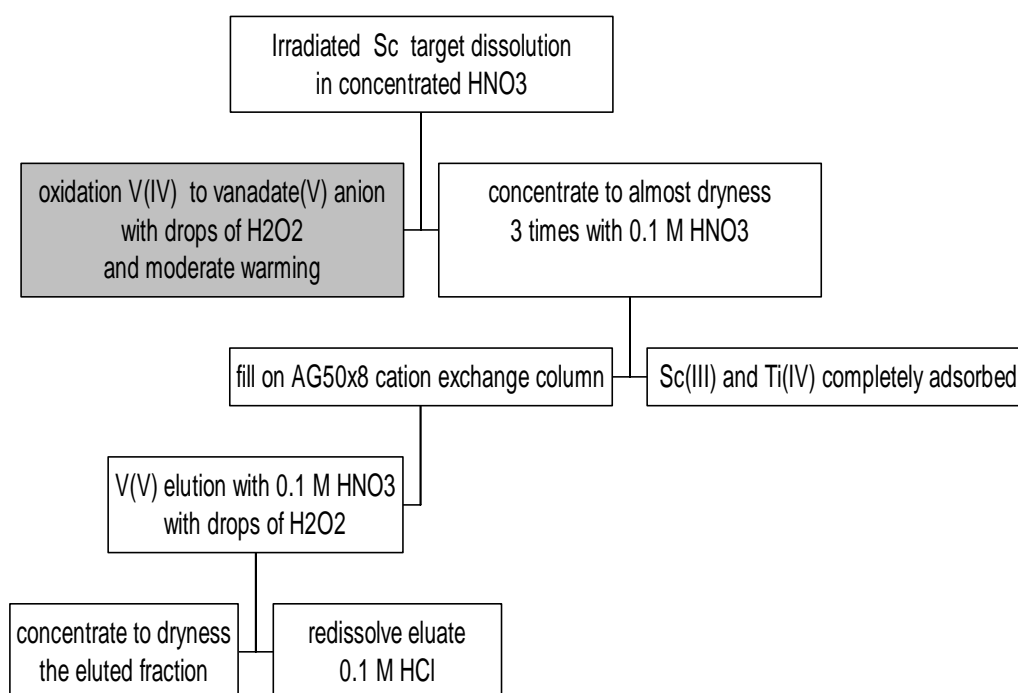


FIG. 2: Simplified scheme of radiochemical separation of ^{48}V from α particle irradiated ^{45}Sc target. The yield of this nuclear reaction is about 46 times lower compared to that obtainable from $^{nat}\text{Ti}(p, xn)$ nuclear reactions.

The yield obtained with this method was of 0.14 GBq C^{-1} ($13 \mu\text{Ci } \mu\text{A}^{-1} \text{ h}^{-1}$), compared to the yield of 6.2 GBq C^{-1} ($600 \mu\text{Ci } \mu\text{A}^{-1} \text{ h}^{-1}$) of the $\text{Ti}(p, xn)$ route. Nevertheless, despite the yield of a factor 46 lower in respect to the other, the advantages of a fast radiochemistry are remarkable. The radionuclides identified in the HPGe γ spectra after a few hour cooling, were ^{48}V , $^{44\text{m}}\text{Sc}$ ($t_{1/2} = 2.44 \text{ d}$), ^{46}Sc ($t_{1/2} = 83.82 \text{ d}$) and ^{47}Sc ($t_{1/2} = 3.35 \text{ d}$)^{10,11}.

The method was based on oxidation of V(IV) to V(V) by H_2O_2 in nitric medium, followed by one step elution of vanadium(V) anion with solvent front with 0.1 M HNO_3 as eluent, from a cation exchange resin (Bio-Rad, AG50Wx8, 100-200 mesh, 7x40 mm), while Sc(III) cations are strongly adsorbed onto the resin bed. The radiochemical yield in respect to ^{48}V was 90 %. The A_S of ^{48}V determined by INAA via ^{52}V was of the order of $37 \text{ MBq } \mu\text{g}^{-1}$.

The decontamination factor from Sc target was about 10^6 and was determined by INAA via $^{45}\text{Sc}(n, \gamma)^{46}\text{Sc}$ nuclear reaction (60 ng in 2 mL of final solution). 60 GBq (1.6 mCi) of ^{48}V have been produced at the EOCP, after a 24 hour irradiation with an α beam current of $6 \mu\text{A}$.

The very simple scheme of separation adopted is shown in FIG. 2. This second method presents the remarkable advantage that there is no production of any radionuclidic impurity of the long-lived and no- γ emitter $^{49}\text{V}^{10,11}$.

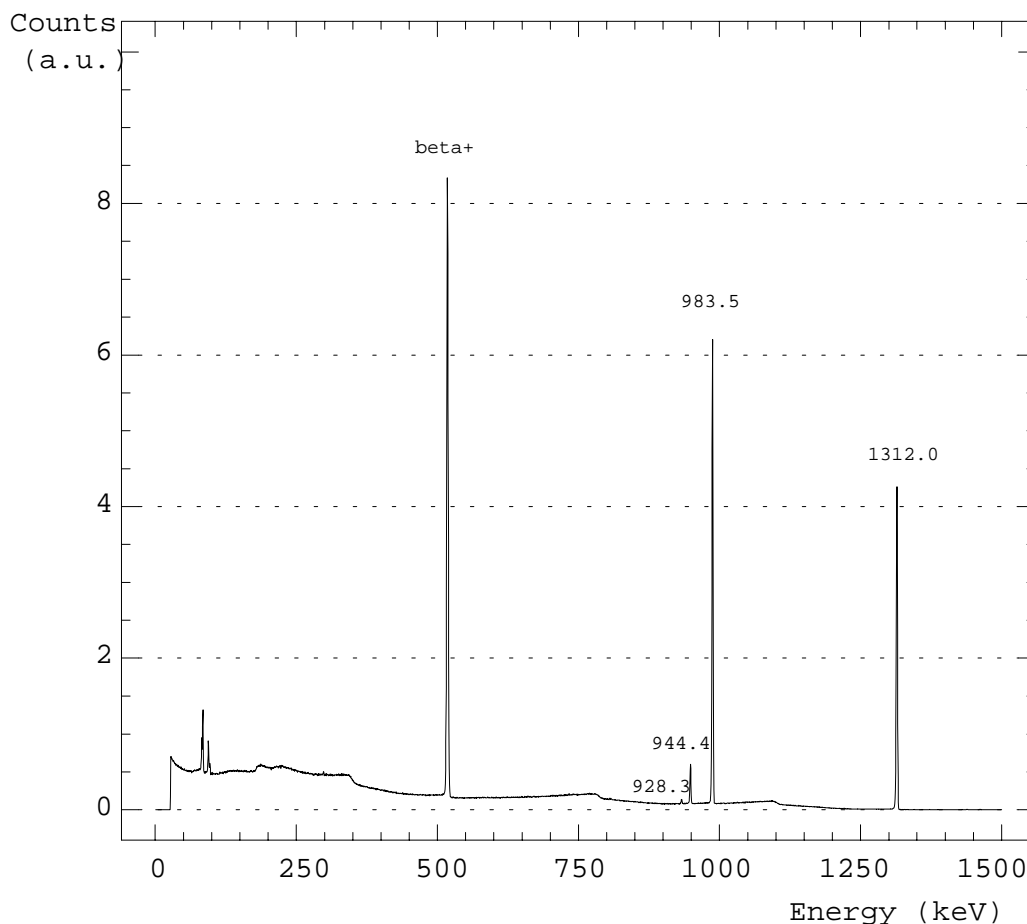


FIG: 3: HPGe spectrum (in a.u.) of a radiochemically pure ^{48}V fraction at the EOCP. No other γ emissions are detectable, even if some long-lived ^{49}V is present in very minute amounts (see text). No peaks are detectable at energies higher than 1500 keV. ^{48}V decays also by positron emission, thus a strong annihilation peak at 511 keV is present.

No titanium radionuclides were detectable in HPGe spectra, as was confirmed and verified by *spiking* the solutions with ^{45}Ti (i.e. cyclotron produced via $^{45}\text{Sc}(p,n)$ reaction) and ^{44}Ti , purchased from Amersham (UK). This result was explained by the oxidation of titanium traces by H_2O_2 to the Vaska's Type hydroxoperoxotitanium(IV) aquacation $[\text{Ti}(\text{O}_2)(\text{OH})(\text{OH}_2)]^+$, which is the dominant cationic species at $\text{pH} < 1$ in the nitric medium used for scandium target dissolution^{14,27,28}. In FIG. 3 is reported an HPGe spectrum of ^{48}V ; in practice both methods adopted led to a very high radionuclidic purity radiotracer, even if in the case of $^{\text{nat}}\text{Ti}(p,xn)$ nuclear reaction a small amount of the no- γ emitter ^{49}V is always produced in small amounts.

3.2.1 High specific activity ^{52g}Mn radiotracer production by $^{nat}\text{Cr}(p,xn)$ nuclear reaction

Manganese-52g ($t_{1/2} = 5.591$ d)^{10,11}) is a medium-lived radionuclide of Mn suitable for experiments envisaged. It can be obtained by activation of ^{nat}Cr target of natural isotopic composition, via both (p,xn) and (d,xn) nuclear reactions. In practice, during Cr activation the short-lived metastable level ^{52m}Mn is also produced ($t_{1/2} = 21$ min)^{10,11}), which contributes *slightly* by decaying by Isomeric Transition de-excitation (1.75 %)^{10,11}) to the ground level ^{52g}Mn . After a detailed study on nuclear reaction cross-sections available in the literature²⁵), we concluded that, as a consequence of Cr isotopic composition (TAB. 2), no advantaged would be obtained by using deuteron beams^{8,9}). Finally, in a classical AVF cyclotron the deuteron beam energy is the half compared to that of protons. The only advantage of using deuteron beams is that due to the higher stopping power of deuteron in materials compared to protons, a thinner Cr target could be irradiated to obtain the same energy loss corresponding to a lower amount of Cr and stable Mn carrier in the final radioactive preparation.

Moreover the $^{52}\text{Cr}(d,n)$ nuclear reaction leads to the long-lived radioisotopic impurity ^{53}Mn ($t_{1/2} = 3.7 \cdot 10^6$ a)^{10,11}), that is undesirable in any case.

The *thick-target yield family of curves* reported in FIG. 4 was obtained by analytical integration of thin-target excitation function of $^{nat}\text{Cr}(p,xn)^{52g}\text{Mn}$ nuclear reactions taken from the literature, as a function of both incident proton energy (MeV) and energy loss ΔE (MeV) into target itself^{8,9}).

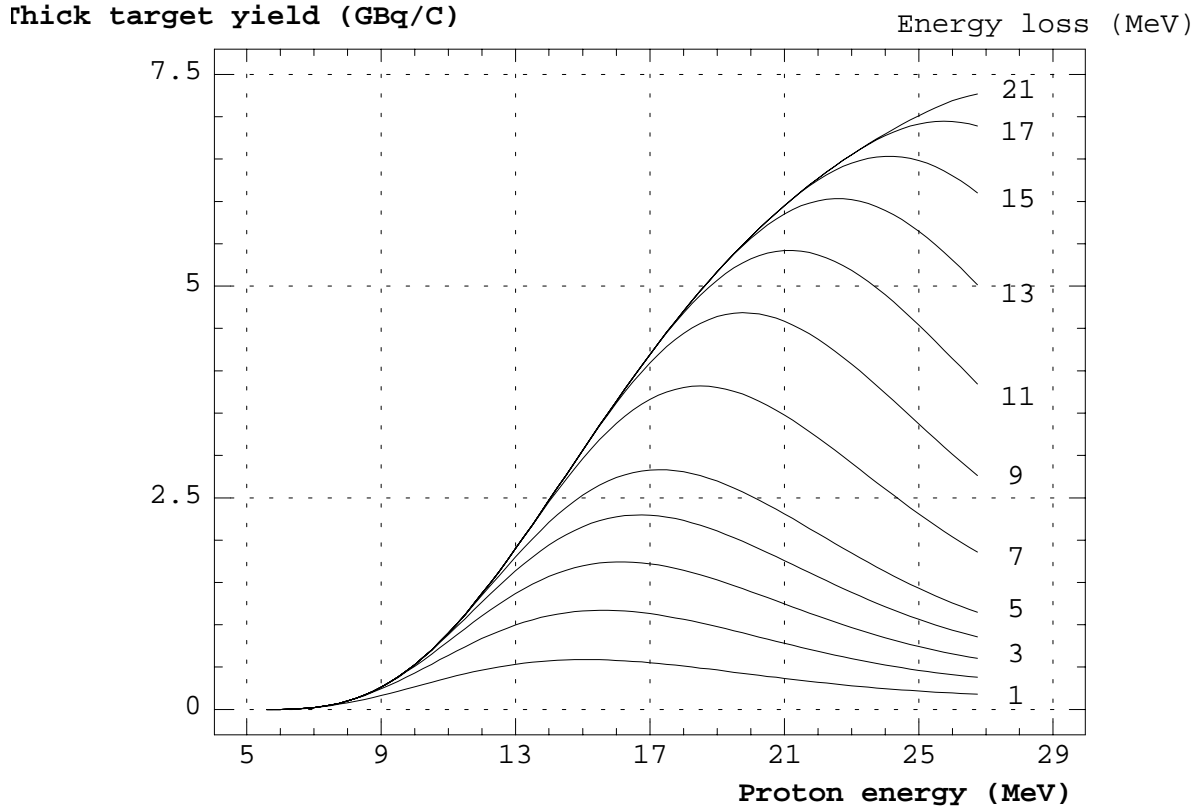


FIG. 4: Thick-target yield in GBq C^{-1} ($1.0 \text{ MBq C}^{-1} \equiv 3.6/37 \mu\text{Ci } \mu\text{A}^{-1} \text{ h}^{-1}$) for production of ^{52g}Mn by proton-induced nuclear reactions on Cr target of natural isotopic composition.

The *family* of yield curves shown in FIG. 4 presents a well shaped locus of the maxima, corresponding to couples of values of incident proton energy E (MeV) on the Cr target and energy loss ΔE (MeV) into the target itself, which allows optimizing production yield minimizing at the same time the mass Cr target thickness (amount of irradiated material).

The irradiated Cr target was dissolved in conc. HCl, brought to dryness and re-dissolved in the minimum amount (a few mL) of 1 M HCl, containing 1000 ppm of Fe(III) as iso-dimorphous carrier for Mn(IV)^{4,6,7,27}. Mn(IV) was *co-precipitated* almost quantitatively with Fe(OH)₃ by addition of an excess of 2.5 M NaOH solution, previously saturated with Br₂.

The bulk of Cr(VI), that was internally labeled by ⁵¹Cr obtained by side nuclear reactions (TAB. 1), remained in the supernatant and discharged. The Fe(OH)₃ iso-dimorphous carrier was centrifuged and re-dissolved in 6 M HCl. Fe(III) was extracted three times in diethyl ether, while ^{52g}Mn remained almost quantitatively into the aqueous phase.

The decontamination of aqueous solution from Fe(III) by L/L extraction was not quantitative and some traces of Fe were found in the final solution. FIG. 5 shows the scheme of radiochemical separation.

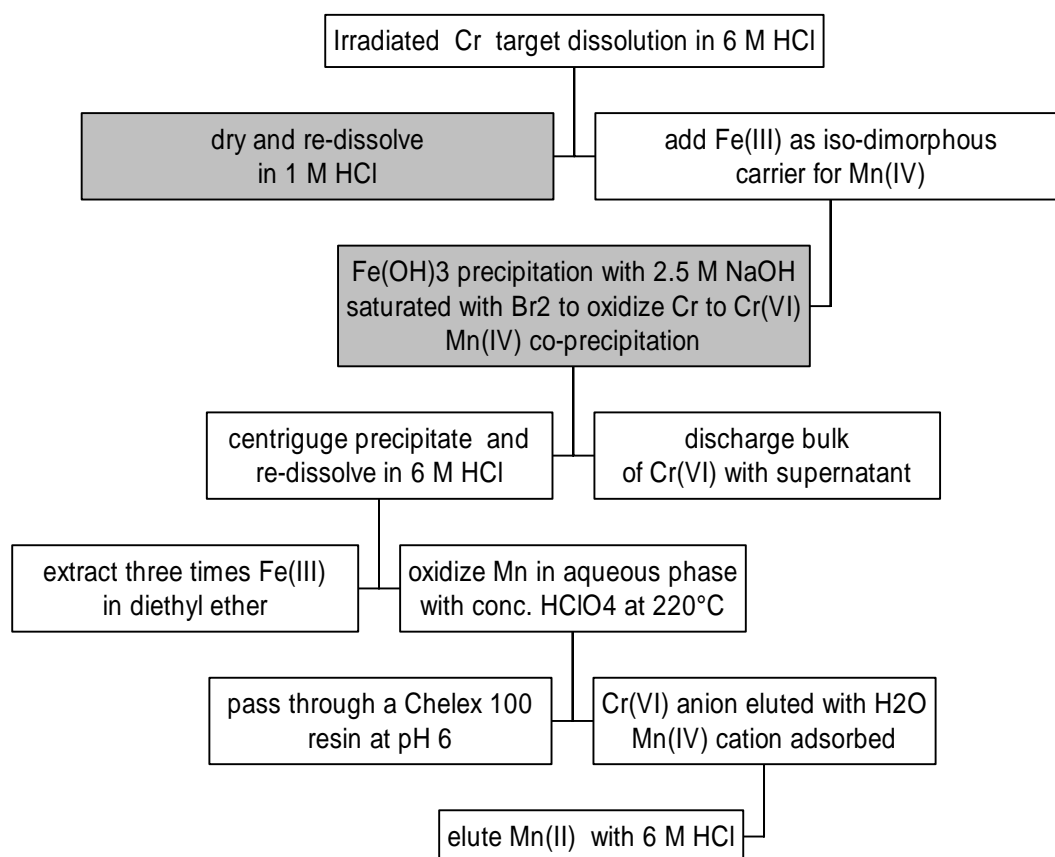


FIG. 5: Scheme of radiochemical separation of No Carrier Added ^{52g}Mn, from proton irradiated ^{nat}Cr target. Due to the addition of Fe(III) iso-dimorphous carrier^{4,6} for co-precipitation of Mn(IV), the final solution contained 30 µg of Fe as impurity (see text).

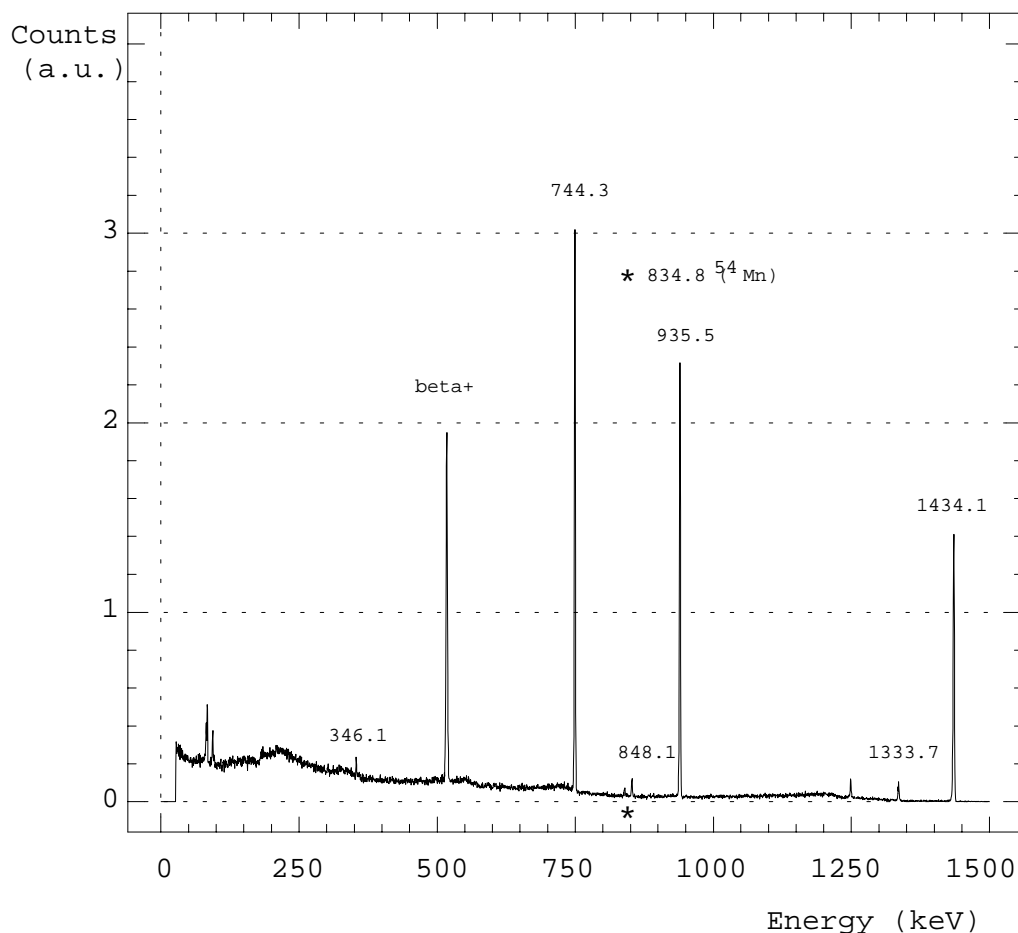


FIG: 6: HPGe spectrum (in a.u.) of a radiochemically pure ^{52}gMn fraction at the EOCP. The asterisk corresponds to the γ emission at 834.5 keV of the only radionuclidic impurity present, which is the long-lived ^{54}Mn (0.3 %) (see text).

The radio-Mn containing the residual Cr was oxidized to Cr(VI) at 220 °C with conc. HClO_4 in a Teflon PFA beaker with graphite bottom (Nalgene, Nalge Co., UK) and passed through a disposable plastic column (Bio-Rad, UK) containing a Chelex 100 weak imminodiacetic cation exchange resin (Bio-Rad, UK, 100-200 mesh, 7x 30 mm) preconditioned at pH 6 with water. While anionic Cr(VI) was almost quantitatively eluted by water with the solvent front, Mn(IV) was quantitatively retained onto the resin bed. Finally, the NCA ^{52}gMn has being eluted by 6 M HCl with a radiochemical yield close to 80 %.

The Mn carrier content was determined by ET-AAS obtaining a A_S of 1.7 MBq μg^{-1} corresponding to an IDF° of 3200. It was not possible using INAA for determination of Mn carrier, due to the large interference of $^{56}\text{Fe}(n,p)^{56}\text{Mn}$ nuclear reaction on Fe. In fact the Fe content in the final solution (4 mL) was of the order of 30 μg , as determined by ET-AAS.

The decontamination factor from Cr target was not very high and of the order of $3 \cdot 10^4$, as determined by both ET-AAS and INAA via $^{50}\text{Mn}(n,\gamma)^{51}\text{Cr}$ nuclear reaction after complete decay of a 300 μL fraction of final solution.

The only radionuclidic impurity identified in the final solution of NCA ^{52}gMn by high-

resolution HPGe spectrometry was ^{54}Mn , in a percentage of 0.3 % at the EOCP. The radio-Mn was present as Mn(II) cation, as verified by testing with anionic (AG1x8) and cationic (AG50Wx8) ion exchange resins (Bio-Rad disposable, 7x 20 mm resin bed). In FIG. 6 is shown a high-resolution HPGe spectrum of ^{52g}Mn fraction after radiochemistry.

3.2.2 High specific activity ^{56}Mn radiotracer production by $^{55}\text{Mn}(n,\gamma)$ nuclear reactions

Manganese-56 presents a very short half-life ($t_{1/2} = 2.5785 \text{ h}$)^{10,11}, thus its $S_A(\text{CA})$ obtained by neutron capture reaction on natural ^{55}Mn target that is mono-isotopic, is acceptable for metallo-toxicological studies, even if its IDF° at the EOCP is poor (TAB. 1).

The specific activity in Bq kg^{-1} produced for radiative neutron-capture nuclear reactions (n,γ), is calculated theoretically by Eqs. (2, 4 and 5), under the acceptable assumption that no target material is consumed by transmutation during neutron irradiation^{4,29,30}:

$$A_S(\tau,t) = f [N_{\text{Av}} M^{-1}] \Phi \sigma [1 - \exp(-\lambda \tau)] \exp(-\lambda t) \quad (4)$$

$$\equiv f [A_S(\text{CF}) \lambda^{-1}] \Phi \sigma [1 - \exp(-\lambda \tau)] \exp(-\lambda t) \quad (5)$$

where: σ ($\text{m}^2 \text{ neutron}^{-1}$) is the *average* reaction cross-section, M (kg mol^{-1}) is the *atomic mass* of ^{55}Mn , f is the isotopic fraction of irradiated nuclide in the target material ($1 \geq f \geq 0$, $f = 1.00$ in case of ^{55}Mn), Φ ($\text{neutron m}^{-2} \text{ s}^{-1}$) is the *average* neutron flux density, τ (s) is the irradiation time under the assumption of a constant flux density, t (s) is the waiting (or cooling) time from the EOB and N_{Av} is the Avogadro's number with proper units.

Ultra-high purity (4N5) powdered metal ^{55}Mn targets of natural isotopic composition (100 mg), were irradiated for 8 hours in the central channel facility of TRIGA MARK II thermal research reactor of the University of Pavia, Italy, with a neutron flux density of $9 \cdot 10^{16} \text{ n m}^{-2} \text{ s}^{-1}$. The targets were sealed in high-purity quartz vial (Supra-Sil), previously leached with boiling conc. HNO_3 . After irradiation, the quartz vials were leached from external contamination with HNO_3 and then broken.

The Mn metal powder was dissolved in HNO_3 , then brought to dryness three times with conc. HCl and finally re-dissolved in diluted HCl and neutralized by NaOH solution. The experimental A_S of ^{56}Mn was determined by simple calculation, as the ratio between the activity produced and the amount of irradiated Mn powder, obtaining a good agreement with theoretical value. Any addition of carrier through chemicals or consumption of ^{55}Mn target during irradiation has been considered negligible in present case.

3.2.3 High specific activity ^{54}Mn radiotracer production by $^{59}\text{Co}(p,\alpha d)$ nuclear reaction

During irradiation of ^{59}Co target (i.e. that is mono-isotopic) by proton beams for production of ^{57}Ni and ^{56}Ni radiotracers, through $^{59}\text{Co}(p,xn)$ nuclear reactions, ^{54}Mn ($t_{1/2} = 312.2 \text{ d}$)^{10,11} is produced in a parasitic way via $^{59}\text{Co}(p,\alpha d)$ nuclear reaction, even with very low yield due to its fairly low cross-section and long half-life.

In practice, we retained easier and cheaper purchasing this radionuclide on the market (Amersham, UK).

3.3.1 High specific activity $^{201,202}\text{Tl}$ radiotracer production by $^{nat}\text{Hg}(p,xn)$ nuclear reactions

By proton irradiation on Hg target of natural isotopic composition, a complex mixture of radionuclides of different half-life and decay mode is produced. Among these radionuclides, two present suitable characteristics for environmental and metallo-toxicological studies: ^{201}Tl ($t_{1/2} = 73.1$ and ^{202}Tl ($t_{1/2} = 12.23$ d), while ^{200}Tl ($t_{1/2} = 26.1$ h) and ^{199}Tl ($t_{1/2} = 7.42$ h)^{10,11}) that are also formed with high yield present an half-life too short for some experiments on laboratory animals. In fact the biological half-life of Tl(I) in living organisms is of the order of 10 days. The no- γ emitter and long-lived ^{204}Tl ($t_{1/2} = 3.78$ a)^{10,11}) is produced too, even with negligible yield. In practice, after a proper cooling time from the EOB, a mixture of ^{201}Tl and ^{202}Tl is obtained. This mixture of two radionuclides can be used in principle for metallo-toxicological experiments, under the condition that a high-resolution γ -spectrometric technique is adopted. Nevertheless, with an appropriate choice of both cooling time and irradiation conditions (i.e: proton energy E, energy loss ΔE into the Hg target, target enrichment), it is possible obtaining each of these radionuclides with a suitable degree of radionuclidic purity. The longer-lived ^{202}Tl can be obtained by simple cooling of all other short-lived radionuclides, after a proper choice of irradiation parameters.

Conversely, ^{201}Tl can be obtained with a suitable degree of radionuclidic purity by using a highly enriched ^{202}Hg as target material (TAB. 2). The choice of this target was based mainly on a cost/benefit choice. In fact, the natural percentage of ^{202}Hg is fairly high (29.86 %). The best radionuclidic purity obtainable by irradiating a 98.6 % enriched ^{202}Hg target was 97 %. No advantages are gained by using a higher enrichment, because the only radionuclidic impurity present after a proper cooling time is ^{202}Tl whose half-life is longer. The by-production of ^{202}Tl cannot be avoided, because it is obtained through $^{202}\text{Hg}(p,n)$ nuclear reactions, whose cross-section tail in the high proton energy region cannot be avoided. An alternative method, that were not investigated, is the production of ^{201}Tl by $^{201}\text{Tl}(p,n)$ reaction on highly enriched ^{201}Hg that is very expensive.

Both natural and enriched Hg targets have been irradiated in a special water cooled target holder made of tantalum, with a thin tantalum window (25 μm thick), and an “O” ring sealing. The system proved suitable for irradiation with proton beam currents up to 5 μA , with a thick-target yield of 14 GBq C^{-1} (1.4 mCi $\mu\text{A}^{-1} \text{h}^{-1}$) in the energy range from 19 to 13 MeV.

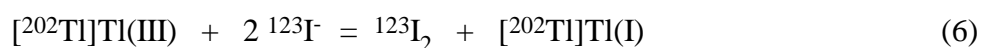
The radiochemical separation of Tl radionuclides from Hg target and Ta target holder was very easy and effective. Enriched Hg target was recovered quantitatively. Both Hg and Ta have been leached three times with very small amounts (1 mL) of 3 M HCl. The recovery of Tl was almost quantitative. In order to improve the radionuclidic purity of radio-Tl from possible metallic species coming from both Hg target and Ta holder a further purification step was inserted, based on oxidation of Tl(I) to Tl(III) by addition of drops of H_2O_2 .

The Tl(III) chlorocomplexes (probably a mixture of tetrachloro and exachloro complexes) have been extracted twice in diethyl ether from 6 M HCl and then back-extracted in very diluted HCl. The overall radiochemical yield for radio-Tl was 90 %. No other γ emitters were identified in final solution by high-resolution HPGe spectrometry.

Tl(I) cation was obtained by bubbling SO_2 into solution, while Tl(III) was obtained by re-oxidation by Cl_2 saturated water. The radiochemical purity was tested by paper radio-

chromatography (Berthold Thin-Layer Scanner, Switzerland) in acetone/water medium, in phosphate buffer, with $R_f[\text{Tl(I)}] = 0.0$, $R_f[\text{Tl(III)}] = 0.96$. If no oxidizing agent is added, one more Tl(III) chemical form was detected with $R_f = 0.62$.

In order to measure the experimental value of A_S , use was made of ET-AAS and stripping voltammetry, obtaining a value of $800 \text{ MBq } \mu\text{g}^{-1}$ for ^{201}Tl , and $200 \text{ MBq } \mu\text{g}^{-1}$ for ^{202}Tl , with IDF° of the order of 5-10. Moreover, in the case of Tl(III), a very sensitive (i.e: 1 ng) “radio-release” analytical technique was developed for determination of Tl carrier, based on the chemical Eq. (6):



The very high A_S $^{123}\text{I}^-$ ($t_{1/2} = 13.2 \text{ h}$)^{10,11} was oxidised to $^{123}\text{I}_2$ that was extracted from the aqueous phase by a very small amount of CCl_4 . To this purpose, NCA $^{123}\text{I}^-$ was produced by $^{124}\text{Te}(p,2n)$ nuclear reaction on highly enriched ^{124}Te target (TAB. 1).

A second effective radioanalytical test for A_S determination of $[^{202}\text{Tl}]\text{Tl(III)}$, was based on the oxidation of $^{48}\text{VO}^{2+}$ aquacation to V(V) anion. The effectiveness of the oxidation process was tested in a higher concentration range by use of EPR spectrometry.

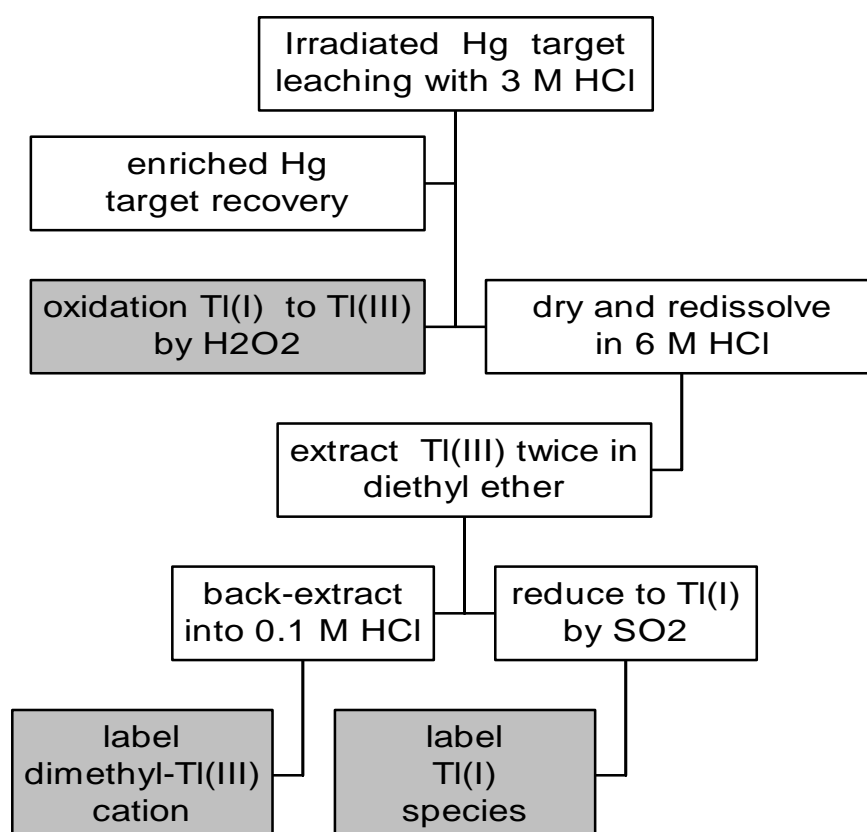
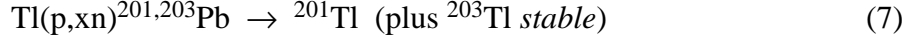


FIG. 7: Simplified scheme of radiochemical separation of $^{201,202}\text{Tl}$ from proton irradiated $^{\text{nat}}\text{Hg}$ and ^{202}Hg -enriched targets.

3.3.2 High specific activity ^{201}Tl production by $^{\text{nat}}\text{Tl}(p,xn)^{201}\text{Pb} \rightarrow ^{201}\text{Tl}$ nuclear route

Thallium-201 is the daughter radionuclide of ^{201}Pb ($t_{1/2} = 9.33 \text{ h}$)^{10,11}, thus a very high purity ^{201}Tl was prepared with an alternative method based on proton cyclotron irradiation on both natural and ^{203}Tl enriched target, via the following nuclear reaction route (Eq. 7):



At the EOB, the ^{201}Pb and ^{203}Pb radionuclides were separated from the activated Tl target (*first radiochemical separation Tl / ^{201}Pb*). After 31.76 hour cooling time, the ^{201}Tl activity reaches a maximum^{29,30}, as shown in FIG. 8 (i.e. the *time of maximum charging* is calculated as: $[\ln 2/t_{1/2(1)} - \ln 2/t_{1/2(2)}]^{-1} \ln [t_{1/2(2)}/t_{1/2(1)}]$, where the $t_{1/2(1)}$ and $t_{1/2(2)}$ are the half-lives of ^{201}Pb and ^{201}Tl respectively) and a *second radiochemical separation* is carried out for separating ^{201}Tl from ^{201}Pb . Only ^{201}Tl is obtained, because the ^{203}Pb , which is produced at the same time by $^{\text{nat}}\text{Tl}(p,n/3n)$ nuclear reactions, decays on stable ^{203}Tl (TAB. 1).

The NCA ^{201}Tl obtained in this way presents a radionuclidic purity larger than 99 % at the EOB. The detailed radiochemical separation of ^{201}Tl from natural and enriched Tl target was published elsewhere³¹.

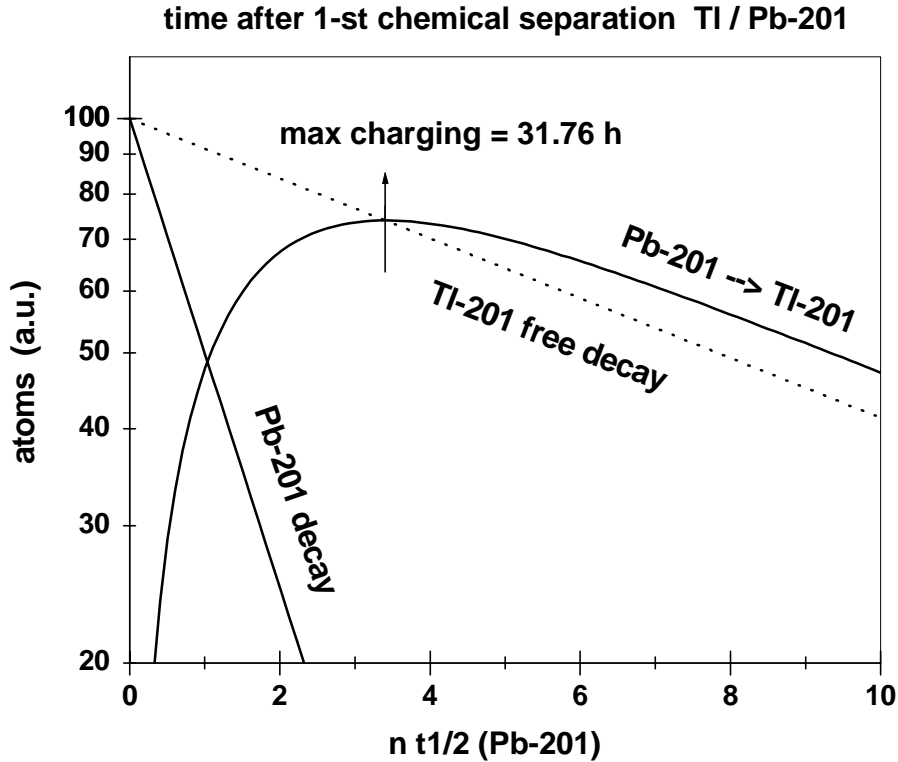


FIG. 8: Decay behavior, in arbitrary units, of ^{201}Pb and ^{201}Tl number of atoms, together with the growth curve of ^{201}Tl charged by decay of ^{201}Pb till to the maximum value 31.76 hours after the first Tl / ^{201}Pb separation. The *time axis scale* is given in ^{201}Pb half-life units.

In order to obtain $[[^{202}\text{Tl}]\text{Tl}(\text{CH}_3)_2]^+$ species, use was made of the method of Gilman and Jones, rescaled to very low concentration³²). An ethereal solution of suspended (but non visible) NCA $[[^{202}\text{Tl}]\text{Tl}(\text{I})\text{Cl}^-]$ chloride was mixed with LiCH_3 and CH_3I in same medium, under dry argon fluxing. The soluble $[[^{202}\text{Tl}]\text{Tl}(\text{III})\text{CH}_3)_2]$ containing solution was hydrolyzed with water obtaining $[[^{202}\text{Tl}]\text{Tl}(\text{CH}_3)_2]\text{I}$. The poorly soluble $[[^{202}\text{Tl}]\text{Tl}(\text{CH}_3)_2]\text{I}$ (adsorbed on vial wall) was solubilized to $[[^{202}\text{Tl}]\text{Tl}(\text{CH}_3)_2]^+$ cation by stirring the solution in a μ -vial with AgF and $\text{Ag}(\text{CH}_3\text{COO})$ for a few hours, obtaining similar results.

Experiments on laboratory animals showed a very similar behaviour between $\text{Tl}(\text{I})$ and $[[^{202}\text{Tl}]\text{Tl}(\text{CH}_3)_2]^+$ cations, while the biokinetics of inorganic $\text{Tl}(\text{III})$ species (probably anionic chlorocomplexes) proved quite different. The studied performed led to the conclusion that *in-vivo* metabolic methylation is an effective de-toxification mechanism for the Tl species.

3.4 Multiple labeling experiments with thallium and manganese chemical species

Whenever different HSARNs of the same element are available, it is possible to carry out *multiple labelling* experiments. In practice, different inorganic or organo-metallic forms of the same element of environmental or toxicological interest are labelled with different radionuclides and then administered at the same animal or cell culture. This procedure can be carried out with different aims: **a.** evaluation of *synergistic effect* of different chemical species of either the same or different elements. **b.** study of the *saturation mechanism* of chemical species in cell organelles and nuclei, as well as animal organs, tissues, body fluids and compartments. **c.** experimental measurement of the *adsorption* and *desorption rates* (internalisation and externalisation) and *repartition* of chemical species in cell cytosol, organelles and nuclei. **d.** accurate evaluation of *dose-effect* relationships of chemical species as a function of different biological and environmental conditions.

FIGS. 9 and 10 show the simplified schemes of multiple labelling experiments performed on cell cultures and laboratory animals with Mn and Tl radiotracers respectively.

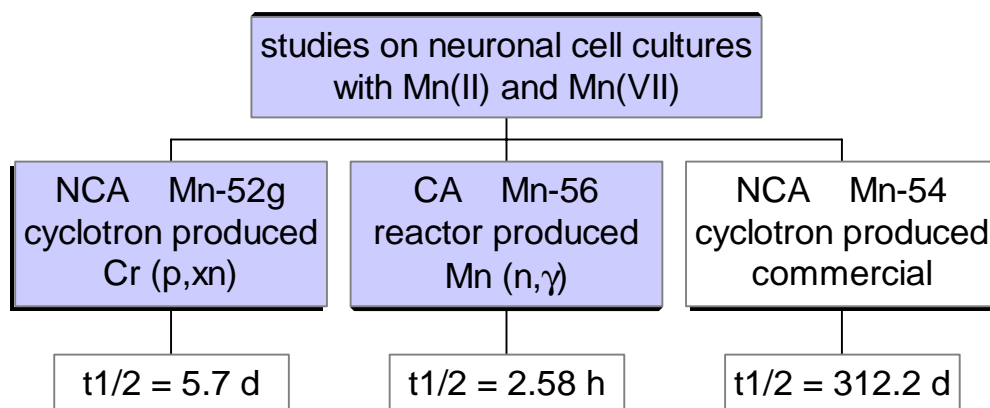


FIG. 9: Triple labelling experiments were carried out by either simultaneous or sequential administration to cell cultures of three different gamma emitters of manganese, in $\text{Mn}(\text{II})$ and $\text{Mn}(\text{VII})$ oxidation states.

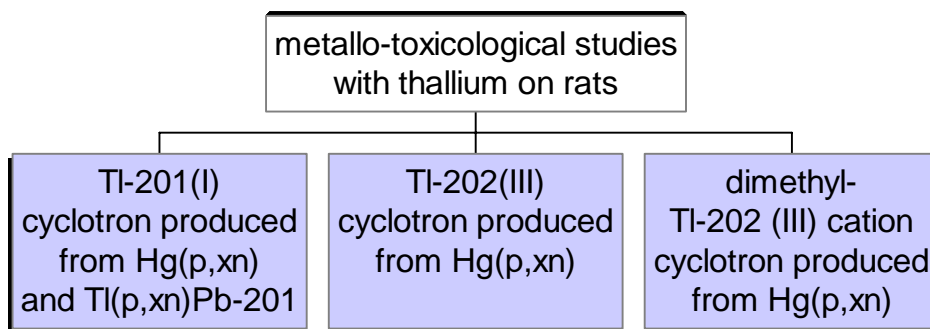


FIG. 10: Metallo-toxicological studies were carried out by administration of different chemical forms of Tl(I) and Tl(III) labelled with ^{201}Tl and ^{202}Tl , to laboratory animals.

4 CONCLUSIONS

Most elements are present in the echo-systems coming from natural sources, while others are introduced into the environment by human activities in increasing amounts. While toxicology of most elements at *high doses* is known since a long time, it is very relevant to assess the exposure of living organisms to different chemical forms of same element at *ultra-trace level*, that are rather unknown. The use of *medium energy cyclotron* and *thermal nuclear reactor* allows producing very high specific activity radionuclides, HSARNs, for environmental, toxicological, occupational studies about the long-term exposure to low doses (LLE) of ultra-trace elements present in the echo-systems. Specific activities A_S in the range of $\text{MBq } \mu\text{g}^{-1}$ to $\text{GBq } \mu\text{g}^{-1}$ are achievable; this means that the experiments can be carried out in the sub-nanogram concentration level, i.e. *nanochemistry*. Moreover, the HSARNs allow labelling of increasing amounts of different chemical forms of toxicological interest, with the possibility to obtain *dose vs. effect* relationships on both cell cultures and laboratory animals. A suitable choice of different radiotracers allows carrying out *multiple labelling* experiments.

Two different nuclear radiochemical methods for production of No Carrier Added ^{48}V were developed and presented. Nuclear radiochemical methods were developed to produce NCA ^{52}gMn and CA ^{56}Mn , while the long-lived ^{54}Mn , even if obtainable by cyclotron irradiation in a parasitic way, was purchased on the market. Different nuclear radiochemical methods were developed for production of ^{201}Tl and ^{202}Tl , starting by different Hg and Tl metallic targets of natural and enriched isotopic composition.

High-resolution gamma spectrometry by HPGe detectors connected to MCA and beta spectrometry by liquid scintillation counting (LSC), allow determination of radionuclidic purity of the tracer, as well as determination of radiochemical yield of processing procedures of irradiated targets, allowing both qualitative and quantitative analysis of activated targets and radiochemistry fractions. Conversely, beta spectrometry by LSC is intrinsically characterised by low-resolution capability, due to continuous spectra of beta emitters, but presents a very high counting sensitivity. Elemental analysis techniques like ET-AAS, ICP-ES, INAA, CSV and ASV, combined with high-resolution γ -spectrometry by HPGe detectors and β -spectrometry by LSC, allowed experimental determination of NCA *specific activity*, A_S

as well as chemical purity of different radiotracers. Very low *isotopic dilution factors*, IDF were obtained for both V and Tl radiotracers, while in case of ^{52}gMn an IDF^o of some thousands was achieved. In the case of ^{56}Mn , the radiotracer was obtained by neutron capture reaction in nuclear reactor. Thus, in this last case a CA radiotracer was obtained, even if its specific activity was sufficient for application envisaged due to the very short half-life of radionuclide itself. The accurate knowledge of nuclear reaction excitation functions for both radionuclide of interest and radioisotopic impurities is a fundamental tool for optimising radionuclidic purity, yield and specific activity of radionuclide concerned^{8,12,33-37}).

5 ACKNOWLEDGEMENTS

Financial support from Italian INFN (V Group) and MIUR (40 %, 60 %) is gratefully acknowledged. The fruitful collaboration with Institute for Health and Consumer Protection, IHCP of JRC-Ispira, Varese, European Commission, CNR, Pavia and ENEA, Italy, is going on with significant scientific results, since the beginning of the '70-ties of '900.

6 REFERENCES

- (1) E. Sabbioni, L. Goetz, C. Birattari, M. Bonardi, *Sci. Total Env.*, **17** (1981) 257-276.
- (2) M. Bonardi, Produzione di radioisotopi ad elevata attivita` specifica con il Ciclotrone AVF dell'Universita` di Milano, **INFN/TC-82/15**, SIS-Pubblicazioni, Frascati, Roma, Italy, 1982.
- (3) M. Bonardi, F. Groppi, C. Birattari, D. Arginelli, *Ann. Chim.*, **92** (2001) 795-813.
- (4) An. N. Nesmeyanow, *Radiochemistry*, MIR Publishers, Moskow, Russia, 1974.
- (5) A. P. Wolf, T. J. Tewson, M. J. Welch, *J. Nucl. Med.*, **22** (1981) 392-393.
- (6) M. Bonardi, F. Groppi, Masurio-99m, masurio-99g, renio-186g e renio-188g: radioelementi chimici isomorfi, ma con attivita' specifica e proprieta' chimico-fisiche differenti. Storia e produzione di radiotraccianti. Metodiche di produzione e controllo di qualita', **INFN/TC-01/04**, SIS-Pubblicazioni, Frascati, Roma, Italy, 2001.
- (7) M. Bonardi, F. Groppi, *Microchem. J.*, **73/1-2** (2002) 153-166.
- (8) M. L. Bonardi, Thin-target excitation functions: a powerful tool for optimizing yield, radionuclidic purity and specific activity of accelerator produced radionuclides, 14-th Radiochemical Conference, Marianske Lazne, Czeck Republic, Invited Lecture, April 2002, *Checkoslovak Journal of Physics*, **In press**.
- (9) M. Bonardi, C. Birattari, F. Groppi, E. Sabbioni, *Appl. Radiat. Isot.*, **57/5** (2002) 617-635.
- (10) E. Brown, R. B. Firestone, *Table of Radioactive Isotopes*, V. Shirley ed., John Wiley and Sons, New York, USA, 1986. ISBN: 0-471-84909-X.
- (11) R. B. Firestone, C. M. Baglin, F. S. Y. Chu, *Table of Isotopes*, 8-th Ed., Update on CD-ROM, John Wiley and Sons, New York, USA, 1998. ISBN 0-471-29090-4.
- (12) TECDOC-1211. *Charged-particle cross-section database for medical radioisotope production*. IAEA, Vienna, Austria, May 2001. At: <http://www-nds.iaea.org/medical/>.
- (13) D. L. Smith, Probability, Statistics, and Data Uncertainties in Nuclear Science and Technology, OECD/NEA, ANS, Illinois, USA, 1991. ISBN: 0-89448-036-7.
- (14) G. J. Leigh, Ed., IUPAC, *Nomenclature of Inorganic Chemistry*, Blackwell Scientific Publisher, Oxford, UK, 1991. ISBN 0-632-02494-1.

- (15) I. Mills, T. Cvitas, K. Loman, N. Kallay, K. Kuchitsu, Eds., IUPAC, *Quantities, Units and Symbols in Physical Chemistry*, Blackwell Scientific Publisher, Oxford, UK, 1993. ISBN 0-632-03583-8.
- (16) M. Gallorini, E. Rizzio, C. Birattari, M. Bonardi, F. Groppi, *Biol. Trace El. Res.*, **71-72** (1999) 209-222.
- (17) G. Gilmore, J. D. Hemingway, *Practical Gamma-Ray Spectrometry*, John Wiley and Sons, New York, USA, 1995. ISBN 0-471-95150-1.
- (18) M. Bonardi, F. Groppi, C. Birattari, *Appl. Radiat. Isot.*, **57/5** (2002) 647-655.
- (19) F. Groppi, C. Birattari, M. Bonardi, L. Gini, *Microchem. J.*, **73/1-2** (2002) 203-211.
- (20) G. T. Peng, *Liquid Scintillation and Cerenkov Counting*, in: D. I. Coomber Ed., *Radiochemical Methods of Analysis*, Plenum Press, New York, USA, 1975, pp.79-149.
- (21) M. Gallorini, C. Birattari, M. Bonardi, L. Magon, E. Sabbioni, *J. Radioanal. Nucl. Chem.*, **160** (1992) 493-503.
- (22) L. Goetz, E. Sabbioni, E. Marafante, J. Edel-Rade, C. Birattari, M. Bonardi, *J. Radioanal. Chem.*, **67** (1981) 183-192.
- (23) E. Sabbioni, M. Bonardi, Li Da-Kang, M. Gallorini, B. Wekerman, M. Castiglioni, *J. Radioanal. Nucl. Chem.*, **134** (1989) 199-208.
- (24) E. Sabbioni, M. Bonardi, M. Gallorini, R. Pietra, S. Fontaner, F. Groppi, *J. Radioanal. Nucl. Chem.*, **160** (1992) 549-561.
- (25) M. Bonardi, M. Gallorini, F. Groppi, S. Saponaro, *Microchem. J.*, **51** (1995) 278-286.
- (26) M. Gallorini, M. Bonardi, F. Groppi, S. Saponaro, *J. Radioanal. Nucl. Chem.*, **193** (1995) 39-47.
- (27) F. A. Cotton, G. Wilkinson, *Chimica Inorganica*, traduzione italiana di: “Advanced Inorganic Chemistry”, 1967, a cura di Bombi G. G., Bresadola S., Cattalini L., Peloso A. Casa Editrice Ambrosiana, Milano, Italy, 1968. pp. 819-829.
- (28) F. A. Cotton, G. Wilkinson, P.L. Gaus, *Basic Inorganic Chemistry*, John Wiley and Sons, New York, USA, 1995, pp. 554-556, ISBN 0-471-50532-3.
- (29) A. Vertes, I. Kiss, Nuclear Chemistry, In: Topics in Inorganic and General Chemistry, Monograph 22, R. J. H. Clark, Ed., Elsevier, Amsterdam, The Netherland, 1987.
- (30) K. H. Lieser, Nuclear and Radiochemistry: Fundamentals and Applications, 2-nd ed., John Wiley and Sons, New York, USA, 2001. ISBN 3-527-30317-0.
- (31) M. Bonardi, *Radiochem. Radioanal. Letters*, **42** (1980) 35-44.
- (32) H. Gilman, R.G. Jones, *J. Chem. Phys.*, **19** (1951) 1427-1432.
- (33) M. Bonardi, The contribution to nuclear data for medical radioisotope production from the Milan Cyclotron Laboratory, IAEA Consultant's Meeting on “Nuclear Data Requirements for Medical Radioisotope Production, Tokyo, April 1987, Invited Lecture, **INDC(NDS)-195/GZ**, IAEA, Vienna, Austria, Jan 1988, pp. 98-112.
- (34) M. Bonardi, C. Birattari, M. Gallorini, F. Groppi, D. Arginelli, L. Gini, *J. Radioanal. Nucl. Chem.*, **236** (1998) 159-164.
- (35) F. Groppi, M. Bonardi, C. Birattari, M. Gallorini, L. Gini, *J. Radioanal. Nucl. Chem.*, **249** (2001) 289-293.
- (36) M. Bonardi, F. Groppi, C. Birattari, C. Mainardi, A. Ghioni, E. Menapace, K. Abbas, U. Holzwarth, M. F. Stroosnijder, *J. Radioanal. Nucl. Chem.*, **257 (1-3)** (2003), **In press**.
- (37) M. Bonardi, C. Birattari, F. Groppi, L. Gini, A. Ghioni, H. S. Mainardi, M. Gallorini, E. Rizzio, E. Sabbioni, *Ann. Chim.*, **93** (2003), **In press**.