# ISTITUTO NAZIONALE DI FISICA NUCLEARE

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# A RAPID IMPROVED METHOD FOR GAMMA-SPECTROMETRY DETERMINATION OF THALLIUM-202 IMPURITIES, IN [THALLIUM-201]LABELLED RADIOPHARMACEUTICALS

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## Abstract

In despite of the cyclotron production method and the efficiency of radiochemical processing adopted, the long–lived *radioisotopic* impurity $^{202}$Tl is always present in [$^{201}$Tl]labelled radiopharmaceuticals (RP) together with other short-living impurities like, $^{200}$Tl. A rapid determination of $^{202}$Tl impurity, is carried out by HPGe gamma spectrometry of $^{201}$Tl samples, shielded by a 5 mm thick envelope of lead. DT correction errors, random pile-ups, Compton continuum and X-ray fluorescence background, are very efficiently avoided and suppressed. Some experimental results on DT correction performances of a commercial HPGe counting chain are reported.

The method described allows determination of $^{202}$Tl impurities in $^{201}$Tl radiopharmaceuticals with high sensitivity and short counting times. The same method could be applied in Nuclear Medicine routine, to determine $^{201}$Tl radioisotopic purity by means of a ionization chamber dose calibrator.

Key Words: $^{201}$Tl , $^{202}$Tl impurity, γ-spectrometry, absorption, sample shielding, dead time

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# 1 INTRODUCTION: THALLIUM-201 FOR RADIODIAGNOSTIC AND TOXICOLOGICAL PURPOSES

Since the late 1970s, the readily commercially available univalent cation [$^{201}$Tl]Tl(I) ($t_{1/2}$ = 72.912 h) in "very high specific activity" No Carrier Added form, is a radionuclide of widespread diffusion, for use in infarction radiodiagnostic and several other cardiovascular and even cerebral Nuclear Medicine investigations by γ-camera and SPECT [1-10]; even if its *whole body excretion half-life* can be considered as long ≈ 10 days [6,11-13]. It decays by EC (100 %) and emits a principal γ-ray at 167.437 keV (10.0 %) greatly Internally Converted (IC) by the K, L, M, N shells of Hg [14-16]. Actually, this emission is a *doublet*, having a small component at 165.887 keV (0.155 %). Thus in the analysis of the γ-spectra, we used a total emission intensity of 10.0 + 0.155 (10.155 %).

Nevertheless, these energies are just in the range suitable for γ-camera and SPECT imaging, as well as for use as a radiotracer to follow the fate of different inorganic and organo-metallic chemical forms of thallium, in short- and medium-term metallo-toxicological studies on both cell cultures and laboratory animals. In this last case, also the longer-lived $^{202}$Tl can be efficiently used for medium-term experiments [11-13,17-19]. $^{201}$Tl theoretical specific activity (SA-CF) in a truly Carrier Free (CF) form is 7.9 GBq/μg (see Tabs. 1 and 2).

**TAB 1**: Theoretical (CF) (GBq/μg) (calculated from Firestone, 1998) and "experimental" IDF° of various thallium radionuclides produced by Tl(p,xn)$^{201}$Pb → , and Hg(p,2n) nuclear reactions on thallium and mercury targets of natural and 98.6 % enriched composition [17,31]. In these cases the specific activity obtained is Nearly Carrier Free (NCF). $^{204}$Tl produced in nuclear reactor by and Tl(n,γ) reactions (see text) presents a very low specific activity, even at saturation irradiation. IDF° is the experimental isotopic dilution factor at the EOCP (see text).

| Tl RN | Target $^{203}$Tl 29.52 % | IDF° | Target $^{203}$Tl 100% | IDF° | Target $^{nat}$Hg 29.86% | IDF° | Target $^{202}$Hg 98.6% | IDF° | SA (CF) |
|---|---|---|---|---|---|---|---|---|---|
| 198m | | | | | | | | | 62004 |
| 198g | | | | | | | | | 21977 |
| 199 | 7.3 | 10.8 | 24.6 | 3.2 | 14.5 | 5.4 | 48.7 | 1.6 | 78.525 |
| 200 | 2.1 | 10.6 | 7.0 | 3.2 | 4.1 | 5.4 | 13.9 | 1.6 | 22.212 |
| **201** | 0.74 | 10.7 | 2.5 | 3.2 | 1.5 | 5.3 | 5.0 | 1.6 | 7.912 |
| 202 | 0.18 | 10.9 | 0.61 | 3.2 | 0.2 | 9.8 | 0.67 | 1.6 | 1.956 |
| 204 | 70E-6 | high ! | 238E-6 | high ! | | | | | 0.0172 |

**TAB 2**: Decay mode, principal gamma emissions and intensities (%) and Carrier Free Specific Activity of main cyclotron produced thallium and lead radionuclides [16].

| Radio Nuclide | T ½ | Decay mode | E-γ (keV) | α (%) | SA (CF) (GBq/µg) |
|---|---|---|---|---|---|
| Tl-199g | 7.42 h | EC+β$^+$ = 100% | 455.46<br>208.20597<br>247.26<br>158.37947<br>many others | 12.40<br>12.28<br>9.30<br>4.96 | 78.525 |
| **Tl-200g** | 26.1 h | EC+β$^+$ = 100% | **367.943**<br>**1205.717**<br>579.298<br>828.230<br>many others | 87.20<br>29.91<br>13.78<br>10.81 | 22.212 |
| **Tl-201g** | 72.912 h | EC = 100% | **167.43**<br>**135.34**<br>**165.88** | 10.0<br>2.565<br>0.155 | 7.912 |
| **Tl-202** | 12.23 d | EC+β$^+$ = 100% | **439.58**<br>520.11<br>959.70 | 91.40<br>0.585<br>0.069 | 1.956 |
| Tl-204<br>↓<br>Pb-204 | 3.78 y<br><br>1.4 E17 y | β$^-$ = 97.10%<br>EC = 2.90%<br>≈ stable | 763.62 EndP<br>**no γ** | | 0.0172<br><br>4.63 E-19 |
| **Pb-201g** | 9.33 h | EC +β$^+$= 100% | 945.96<br>907.56<br>692.37<br>584.55<br>many others | 7.36<br>5.70<br>4.27<br>3.56 | 61.828 |
| Pb-200 | 21.5 h | EC = 100% | 147.63<br>257.17<br>235.62<br>268.38<br>many others | 37.73<br>4.46<br>4.30<br>3.96 | 26.965 |
| Pb-202m | 3.53 h | EC = 9.5%<br>IT = 90.5% | 960.97<br>422.18<br>786.99<br>657.49<br>many others | 91.63<br>85.66<br>49.80<br>32.40 | 162.61 |
| Pb-202g | 5.25 E4 y | EC > 99%<br>α < 1% | **no γ**<br>2547 α | <br>0.01 | 1.25 E-06 |
| **Pb-203** | 51.873 h | EC = 100% | 279.20<br>401.32<br>680.52 | 80.80<br>3.35<br>0.75 | 11.011 |

## 1.1 Specific Activity, SA and Isotopic Dilution Factor, IDF

In practice, No Carrier Added [$^{201}$Tl]Tl is always diluted in a variable amount of both stable and radioactive nuclides of thallium itself (in practice of mass number: A=198-204). The only two stable nuclides of thallium in a target of natural isotopic composition are: $^{203}$Tl (29.524 %) and $^{205}$Tl (70.476 %) [16].

For a radionuclide of decay constant $\lambda = \ln 2 / t_{1/2}$ (s$^{-1}$), of a given chemical element, the Isotopic Dilution Factor, IDF, is a non-dimensional quantity, increasing exponentially with waiting time t (s) after the End Of radioChemical Processing (EOCP), defined as:

IDF (t) = number of atoms of same element / number of atoms of radionuclide of interest =

$$= \text{SA (CF) / SA (t)} = \text{IDF}° \exp(\lambda t) \text{ , that is always } \geq \text{ IDF}° \qquad (1)$$

$$\text{SA(CF)} = \lambda / N_a \qquad (N_a = \text{Avogadro's constant}) \qquad (2)$$

where, according to Alfred P. Wolf (1981) [20], the real specific activity obtainable in NCA form, SA(NCA) is normally lower than the CF one of a factor from a few units up to *several thousands*, as we showed by graphite furnace atomic absorption spectrometry (GF-AAS), inductively coupled plasma optical emission spectrometry (ICP-OES) and anodic stripping voltammetry (ASV).

We obtained Isotopic Dilution Factors at the EOCP (IDF°) ranging from two to some tens, by using appropriate high purity targets, chemicals and teflon-PFA equipment [11,13,17-19,21]. Recently, Al Jammaz and Richard M. Lambrecht (2000) [22] published a comparison of metal content (Tl carrier, Cu and Fe), obtained with different production methods. Thallium concentrations range in the 1-2 μg/ml interval, even if the activity concentration is not reported.

Conversely, the (n,γ) reactor produced $^{204}$Tl (t$_{1/2}$ = 3.78 y; β$^-$ 97.1 %, EC 2.9 %, **no γ**) is very unsuitable for uses in both medicine and environmental toxicology, due to its long half-life and very low specific activity of only 238 GBq/g - obtainable at "saturation" - on a 100 % enriched $^{203}$Tl target ($\sigma_{th}$ = 11.0 barn), with a thermal neutron flux of $10^{13}$ n/s cm$^2$ [23,24]. It is detectable by either LSC or Cherenkov counting in water solution (beta End Point 763.72 keV). Furthermore, $^{204}$Tl decays on the long-lived $^{204}$Pb (t$_{1/2}$ > 1.4 $10^{17}$ y) [16].

Apart the bad kind of emissions, the low specific activity of $^{204}$Tl, does not allow its use on living organisms (both cells cultures, plants, laboratory animals, humans) due to the very high chemical toxicity of thallium [13,25,26] and further chemical considerations (see next sections).

The short-lived $^{199}$Tl (t$_{1/2}$ = 7.42 h; EC + β$^+$ 100 %, medium energy γ-s), was proposed as a radiodiagnostic agent also. It was produced by both proton irradiation on mercury target [27,13] and alpha particle bombardment on thick gold targets [28,29].

Nevertheless, due to its high-energy gamma emissions, we retain it is unsuitable for radiodiagnostic purposes.

## 2 RADIOCHEMICAL PROPERTIES OF THALLIUM IN No Carrier Added (NCA) FORM

Thallium (Z= 81) is a very rare element, present in the echo-systems in trace amounts (0.1-10 ppm in the earth crust) [25,26,16]. It is very poisoning and generally considered unessential to human life. Nevertheless, trace amounts of thallium coming from semiconductor electronic and alloy industry, are present in the environment in different chemical forms, that are metabolised by living organisms in complex ways [13,12].

Thallium chemistry is not very complex and the element exists in two different oxidation states only: (I) and (III), in several inorganic and organo-metallic compounds [25,26,30]. Most Tl(I) compounds present a very low solubility. The ionic radius of Tl(I) cation (144 pm), is quite similar to that of K(I) (133 pm), Rb(I) (148 pm) and that of ammonium cation $NH_4^+$. This property, suggested its use, as [$^{201}$Tl]thallium(I) chloride in No Carrier Added (NCA) form, in physiological solution (sterile and apyrogenic saline; i.e: aqueous sodium chloride solution 0.9 %, pH 5-7), to *label in-vivo* the potassium pool of cardiovascular system [1,7].

Furthermore, the very high specific activity of NCA [$^{201}$Tl]thallium(I) chloride, allows its i.v. injection onto humans, in despite of the high chemical toxicity of thallium and the low solubility of thallium(I) in chloride medium, with a $K_{ps} \approx 3.2 \ 10^{-4} \ (mol/l)^2$ at 37 °C (Korenman (1969), p. 122) [25].

Conversely, thallium(III) oxidation state is quite unstable, but forms several stable halogeno-complexes and organo-metallic compounds in both aqueous and saline acidic solutions[13,25,26,30]. Radio-paper, -TL and/or -liquid chromatography and radio-electrophoresis have been efficiently used to verify its radiochemical purity [31], as well as its stability with storage time [27].

The mass of Tl carrier was generally determined by GF-AAS, ICP-OES, ASV. Viceversa, Neutron Activation Analysis (NAA) presents a too low sensitivity for Tl.

Finally, an extremely sensitive *radio-release* technique, based on the oxidation of NCA [$^{123}$I]iodide anion by Tl (III), to volatile [$^{123}$I]iodine, followed by liquid/liquid extraction in carbon tetrachloride, was used to determine the content of thallium (III) carrier in $^{201,202}$Tl, used to label NCA [$^{201,202}$Tl]dimethyl-thallium cation [13], with a sensitivity of 1 ng of Tl.

In conclusion, its NCA *specific activity* can reach different values, depending on the production and radiochemical separation route adopted.

## 3 THALLIUM-201 PRODUCTION METHOD AND RADIONUCLIDIC PURITY

Unfortunately, the $^{201}$Tl ($t_{1/2}$ = 72.912 h, EC 100%) produced in charged-particle accelerators, is *always* contaminated by variable amounts of $^{200}$Tl ($t_{1/2}$ = 26.1 h, EC+$\beta^+$ 100%), $^{202}$Tl ($t_{1/2}$ = 12.23 d, EC+$\beta^+$ 100%) and even by the short-lived $^{199}$Tl ($t_{1/2}$ = 7.42 h, EC+$\beta^+$ 100%) and $^{198m,g}$Tl. In-fact, many production methods have been developed for this radionuclide, based *mainly* on proton-induced nuclear reactions, due mainly to both cost and technological considerations. In general, due to the lower stopping power and lower specific power dissipated into the target (kwatt/g), high-energy proton reactions are envisaged [32-35]. Nuclear reaction induced by proton, deuteron, alpha, He-3, as well as high-energy proton and

alpha spallation reactions, have been studied [36-50]. We can group them in two main categories:

(1)   *Indirect* nuclear reactions and/or followed by *decay charging* like:

Tl(p,xn), Tl(p,3n), Tl(p,5n), Tl(p,3n+5n)$^{201(m+g)}$Pb $\rightarrow$ , on both natural and enriched $^{203,205}$Tl targets, in cyclotrons of Class II or III [32];

$^{209}$Bi(p,9n)$^{201}$At $\rightarrow$ $^{201(m+g)}$Po $\rightarrow$ $^{201(m+g)}$Bi $\rightarrow$ $^{201(m+g)}$Pb $\rightarrow$ , and natural/enriched $^{206}$Pb(p,xn)$^{201(m+g)}$Bi $\rightarrow$ $^{201(m+g)}$Pb $\rightarrow$ (as a summary (p,xpyn), (p,X) $^{201(m+g)}$Pb $\rightarrow$ ), in higher energy (> 80 MeV) cyclotrons of class III [32]. Some evaluation of experimental data and calculated cross sections by the ALICE [51-53] and other codes like STAPRE and OSCAR, have been carried out by some authors in the proton energy range up to 100 MeV [42,54].

(2)   *Direct* nuclear reactions:

On both natural and enriched solid mercury oxide or liquid mercury targets, such as: $^{nat}$Hg(p,xn) and $^{202}$Hg(p,2n), nuclear reactions were studied [55,37,13,27,45,46,17,18]. Obviously, $^{201}$Tl cannot be produced by direct $^{197}$Au($\alpha$,xn) reactions, but only other less useful thallium radionuclides like: $^{200}$Tl, $^{199}$Tl, $^{2198m}$Tl and $^{198g}$Tl [28].

A compilation of the most reliable cross-section data for $^{201}$Tl production was published recently as an IAEA-TECDOC document (IAEA, 2001) [56].

Furthermore, $^{201}$Tl it is sometimes contaminated by **non** radio-isotopic impurities, like $^{203}$Pb ($t_{1/2}$ = 59.408 d, EC 100 %) and $^{201}$Pb ($t_{1/2}$ = 59.408 d, EC+$\beta^+$ 100 %) and others, whose content is due to radiochemical separation yield of thallium radionuclides from both lead, mercury, bismuth and other parent radionuclides, as reported in [38-41,43,31,50,57].

In Tab. 2 are reported the decay modes and main emissions of the radionuclides concerned with this work.

## 4    N.C.A. Tl RADIOCHEMICAL SEPARATION FROM IRRADIATED TARGETS

The separations used, are based on co-precipitation, ion-exchange chromatography, liquid/liquid extractions, precipitation, electrochemical deposition, thallium volatilisation and several combinations of these radiochemical techniques [2,11,12,13,17, 31,38-40,43,50,55,58-65]. Most efforts have been made to gain a NCA $^{201}$Tl, with Nearly Carrier Free specific activity [20], even if the British Pharmacopoeia (1993) [66] allows a specific activity not lower than 3.7 MBq/μg, with a very "high" IDF of 2138.

Recently, Trtic' and Comor (1999) [67] developed a method based of Tl(III) extraction with butyl acetate. Van der Walt and Naidoo (2000) [57], published a radiochemical separation based on a modified cation/anion exchange chromatography separation method [31].

A completely new method, using a *p-tert*-butylcalix-[4]-arene derivative, as chelating agent, based on thermodinamic stability considerations, has been published recently [22]. In this last case $^{201}$Pb + $^{203}$Pb radionuclidic impurities were removed by washing the organic phase with alkaline water saturated butan-1-ol at pH 10.

Amongst the various possible isotopic and non radioisotopic impurities, the $^{202}$Tl, due to its longer half-life, increases its percentages in [$^{201}$Tl]labelled radiopharmaceuticals, the

longer is the time after the End Of radioChemical Processing (EOCP). Radiochemical purity must be checked to ensure that thallium is present in univalent state, because thallium(III) oxidation state and chemical forms present a quite different metabolic fate [2,4,5,7,27,31].


## 5 ORIGIN OF THALLIUM-201 RADIONUCLIDIC IMPURITIES

In practice, the percentage of radionuclidic impurities, depends on nine physico-chemical parameters:

**a.** *Nuclear reaction* chosen,
**b.** *Enrichment* of irradiated target,
**c.** *Incident projectile energy*,
**d.** *Energy loss in the target* itself,
**e.** *Radiochemical processing* adopted,
**f.** *Irradiation* and *cooling times* from the EOB and the various radiochemical separation steps adopted, EOCP,
**g.** *Storage* and *waiting times* from the EOCP and the time of injection to patient,
**h.** *Presence of stable impurities in target material,* and finally,
**i.** Possible *cross contaminations* due to nuclear medicine *"bad laboratory practice"* [68].

It is evident that in despite of the lower yield, the medium-lived $^{202}$Tl constitutes the main problem from radioisotopic contamination point of view. Remember that the whole body clearance time of thallium in humans is of the order of 10 days. In fact, a few days after the EOCP, any [$^{202}$Tl]labelled RPs must be considered as *expired*. Conversely, whenever is present, $^{200}$Tl constitutes a problem due to its high-energy gamma emissions.

We and other authors showed since many years [31], that in principle it is possible to obtain $^{201}$Tl, with a radioisotopic purity greater than 99.9 % mainly by use of proton induced nuclear reactions on natural and enriched Tl, Pb and Bi targets, and a good choice of both incident proton energy and energy loss in the target itself [31,38-40,43].

Manuel Lagunas-Solar and co-workers, proposed successfully a *twin-target* irradiation system on enriched $^{205}$Tl and $^{203}$Tl for cyclotrons of Class III.

The production method we developed in Milano, based on direct $^{202}$Hg(p,2n) reactions on enriched $^{202}$Hg target, leads to an overall contamination by $^{199}$Tl + $^{200}$Tl + $^{202}$Tl, not lower than 3 % at the End Of an Instantaneous Bombardment, EOIB, with a thick-target yield for $^{201}$Tl, quite similar to that obtainable by the Tl(p,xn) routes [27,45,46].

Nevertheless, the alternative production method we studied, leads to a very high specific activity thallium radiotracer, that can be considered Nearly Carrier Free (NCF), with an IDF° of the order of 2-5 [13,17], at the EOIB [35]. On the other hand, the recent update of USP **24** (2000) [69] is not very strictly and allows the use of $^{201}$Tl, with radionuclidic purity not lower than 95.0 !

It is evident that producing $^{201}$Tl with a radionuclidic purity larger than 95 %, even it is possible in principle, would decrease sharply the production yield, increasing at the same time the unit cost of the radiopharmaceutical compound.

# 6 COMMERCIAL SAMPLES OF [$^{201}$Tl]-THALLIUM CHLORIDE RADIOPHARMACEUTICALS

In our experimental measurements during about 20 years [68], on a *wide range of commercial samples* of [$^{201}$Tl]thallium(I) chloride RP for i.v. injection, we found variable amounts of the various radionuclidic impurities mentioned above. In particular, most of them contain $^{202}$Tl, in percentages varying from 0.5 up to 5 %, *before the expiration* time of the RP itself [68]. Apart the dose to the patients, medical and paramedical personnel and total population, the medium-lived $^{202}$Tl emits some γ-rays of medium energies (**439.56**, 520.13 and 959.7 keV) [16], which contribute in increasing the S/N ratio and the degradation of γ-camera and SPECT images contrast.

Moreover, the emission intensities *ratio* of 439.56 ($^{202}$Tl) to 167.43 keV ($^{201}$Tl) γ-peaks of 0.941/ 0.10 = **9.41**, is a further disadvantage from this point of view.

Conversely, $^{200}$Tl content is negligible in most cases due to its the short half-life and normally does not constitute a problem from both dosimetric and rad-waste point of views.

# 7 COUNTING CHAIN, DATA ACQUISITION AND ANALYSIS

The γ-spectra have been acquired by multichannel analysers, MCAs (EG&G ORTEC, mod. 562, 572 spectroscopy amplifiers and mod. MCB 918A, 919 ADCs) connected to 50 cm$^3$ coaxial HPGe detectors, with intrinsic efficiency of 15 % (EG&G ORTEC), and a peak to Compton ratio of 30:1 at 1332.50 keV, FWHM 2.3 keV ($^{60}$Co point source). We used channels/keV conversion ratio of about 2:1. The liquid samples of [$^{201}$Tl]labelled RP (2 ml) were enclosed in 20 ml volume, 2 mm thick, glass scintillation vials (Beckman, USA).

The point standard sources and the samples were put at 25 cm distance from detector in order to neglect the need of geometry corrections. Moreover, in general, this precaution decreases the probability of random summations and piles ups [70,71]. Nevertheless, in the present case, the RNs under study do not present cascade emissions and their emission energies do not allow escape peak formation.

Finally, in the present study, the absolute value of sample activity was not relevant. Nevertheless, the relative activities of the various RNs, have been measured by use of a calibrated $^{152}$Eu wide energy range γ-source (CIS, France). The spectra have been acquired and analysed by s/w package Gamma Vision 5.2 for Windows (EG&G ORTEC, mod. A66-B32, USA), installed on Pentium II, III, IV 233-1700 MHz, Intel μ-processor based PCs (AST, ACER, Compaq, USA) network (INFN-LASA, Milano).

The efficiency data, obtained by a certified point source of $^{152}$Eu, 41.1 kBq (2 % overall uncertainty) (CIS, CEA, France), have been fitted by both Gamma Vision and s/w package TableCurve 1.10 for Windows (Jandel Scientific, AISN Software, Germany). The spectra have been exported from Gamma Vision format to Windows Excel format (Office 2000 on MS Windows/NT 1998 platform), after conversion to .txt files, by the code ALPI (University of Milano, private). Finally the Excel files have been converted and imported in the graphics and statistical s/w package ORIGIN 5.1 (Microcal Software, Inc., MA, USA).

We used EXCEL and ORIGIN s/w packages for drawing all figures and tables presented in this paper.

## 8    EXPERIMENTAL SET UP TO INCREASE THE SENSITIVITY OF $^{202}$Tl IMPURITY DETECTION

It is evident that by use of a high-resolution gamma spectrometry, with HPGe detector, connected to a MCA, a γ-peak at 439.56 keV (**$^{202}$Tl impurity**) can be easily detected and discriminated by lower energy peaks at 135.34 keV, 167.437 keV (**$^{201}$Tl**) and 357.943 keV (**$^{200}$Tl**). Nevertheless, in practical Nuclear Medicine, it is advisable having an accurate and reliable determination of the impurity content in the shorter counting time as possible. Furthermore, in many Nuclear Medicine departments, high-resolution HPGe detector based spectrometers are not available. In fact, in order to determine the impurity, it is advisable to count a higher activity as possible (a small aliquot of the RP compound) for a short time. But, a total activity greater than some kBq (a fraction of μCi) gives a counting rate of several thousands Hz, mainly due to the **$^{201}$Tl** gamma emissions at **135.34** and **167.437** keV, their continuous Compton spectra towards the lower energies and Hg X-rays.

Moreover, the 10 cm thick Pb shielding of HPGe detector, produces Pb X-rays fluorescence photon back-scattering and electron bremβtrahlung. To reduce this last effect, the HPGe cup was enclosed in a 15 mm thick perspex box (25 x 25 x 25 cm). The most undesirable effects of high counting rates are the increasing of counting dead time, DT, and probability of spurious effects like random summation and pile-ups [70,71]. In fact, it is obvious that these effects lead to an intolerable underestimate of sample activity.
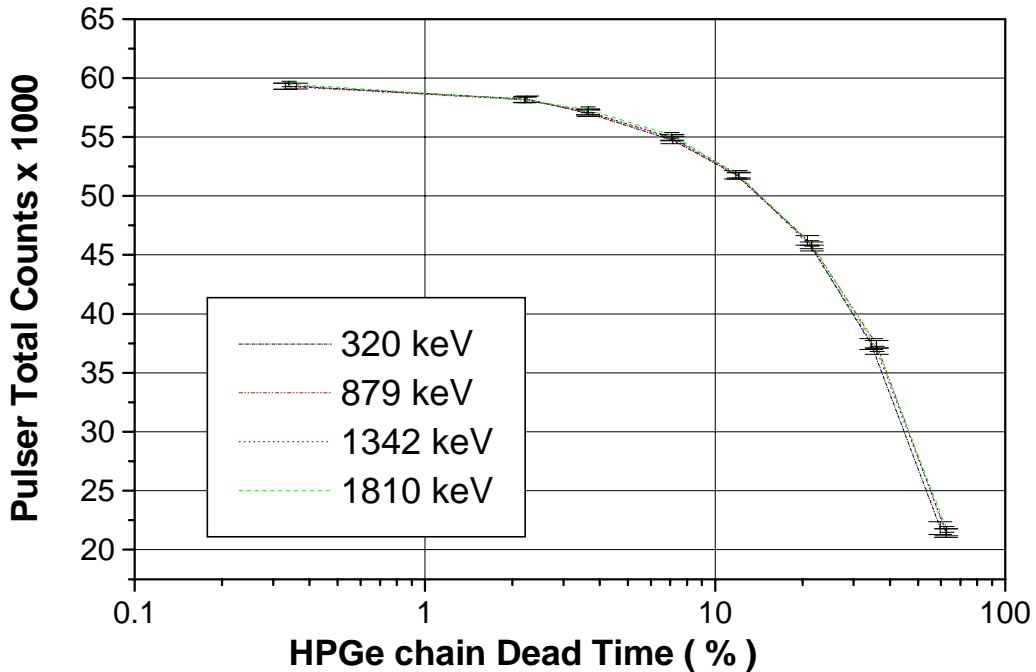


**FIG. 1**: Total peak counts of a Constant Frequency Pulse Generator (set at 98.5 Hz), as a function of counting Dead Time (log %) for the HPGe chain described in the text. The chain dead time, DT was increased by an external $^{152}$Eu gamma source.

**8.1 MCA calibration studies by Constant Frequency Pulse Generator**

It is easy to show, by use of a constant frequency pulse generator (BNC, mod. PB-4, USA) that, with spectroscopy amplifiers like: EG&G ORTEC, mod. 572 and 672, connected to multi-channel buffers like: EG&G ORTEC, MCB 918A or 919, the counting time correction electronics fails for DT values larger than 5-10 % (see Figs. 1 and 2).

Moreover, an unexpected dependence of DT correction electronics vs. pulse generator gain is shown in Fig. 2.

In practice, as a rule for Good Laboratory Practice, in order to have an accurate activity determination, by high-resolution HPGe gamma spectrometry, it is advisable counting small activities (a well known aliquot of radioactive sample), with counting DTs of a few %.

The use of a low energy discriminator, before the spectroscopy amplifier, can eliminate all the lower energy components of both peaks in interest, with significant reduction of DT, but this more sophisticated approach is not used in most Nuclear Medicine departments.
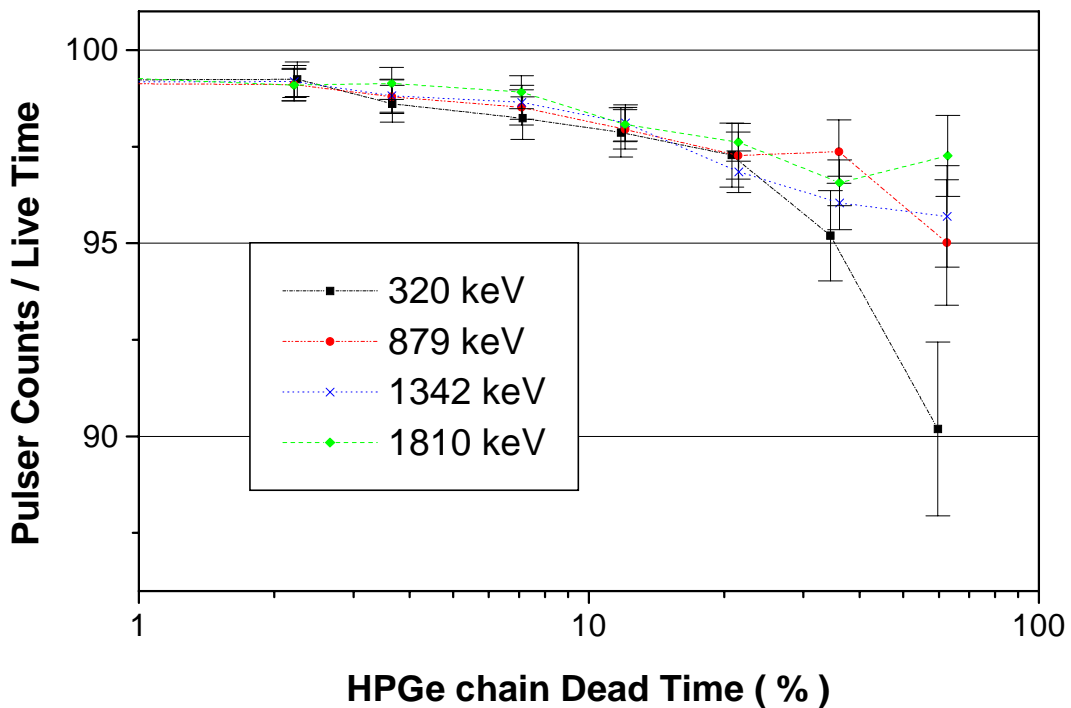


**FIG. 2**: Constant Frequency Pulse Generator counting rate (set at 98.5 Hz), as a function of counting Dead Time (log %) and gain for the HPGe chain described in the text.
At lower pulse generator gain (energy), the DT correction seems less effective

**9    A FEW THEORETICAL CONSIDERATIONS**

As a crude assumption, let us describe the absorption of a parallel photon beam of intensity I°, in different materials of thickness $\Delta x$, with the simplest equation (3):

$$I / I° = 2^{(-\Delta x / d_{1/2})} \tag{3}$$

where: $d_{1/2}$ is the half-thickness of the absorber [16], calculated by use of the atomic photon cross-sections [72], that include contributions from both the coherent (low energy elastic Rayleigh $\div Z^2$, Thompson $\div Z$) and incoherent (inelastic Compton $\div Z$) scattering, as well as the absorption by photoelectric effect ($\div Z^{3.5}$, $Z^4$) and by electron-positron pair production ($\div Z^2$) in the higher energy region ( > 1.022 MeV). Photonuclear reactions ($\div Z$, $Z^2$) and resonance absorption effects ($\div Z$) are not included. For a more deep discussion see: [73-79].

For a couple of photons of different energy, the ratio between the two absorption coefficients can be defined as by equation (4):

$$\mathbf{R} = (I_1 / I_1°) / (I_2 / I_2°) = 2^{-\Delta x (1/d_1^{1/2} - 1/d_2^{1/2})} = 2^{-\Delta x K} \tag{4}$$

Some calculated values of **R** are reported in Tab. 3 for different Z element absorbers. Secondary effects, produced by the scattering of emitted photon and electron beams both into the absorber itself and detector, as well as the fact that both source and detector have not point geometry, have been considered also [73].

These effects, must be taken into account mainly to determine the effective exposure of a gamma/electron source outside a shielding material. Nevertheless, the experimental results obtained in this work, showed that these effects would be neglected for our purposes. Thus, in order to both reduce the pile-up and DT correction errors due to the high counting rate, we counted the $^{201}$Tl ($^{202}$Tl, $^{200}$Tl) samples, shielded by a 5 mm thick cyclindrical envelope of lead.

With this counting arrangement, the overall counting rate is decreased, while the ratio between the high-energy peak region and the low energy one is increased significantly.

**TAB. 3**: Calculated absorption ratios, **R,** between the principal $\gamma$-emissions of $^{201}$Tl at 167.43 keV (10.0 %) and $^{202}$Tl at 439.58 keV (91.4 %), for different thickness of element absorbers.

| R | | | | | | |
|---|---|---|---|---|---|---|
| DX ( mm ) | Pb 82 | Sn 50 | Cu 29 | Al 13 | C 6 | Be 4 |
| 1.0 | 0.6098 | 0.9056 | 0.9532 | 0.9919 | 0.9932 | 0.9955 |
| 2.0 | 0.3718 | 0.8202 | 0.9086 | 0.9838 | 0.9864 | 0.9910 |
| 3.0 | 0.2267 | 0.7428 | 0.8661 | 0.9758 | 0.9797 | 0.9865 |
| 4.0 | 0.1382 | 0.6727 | 0.8256 | 0.9679 | 0.9731 | 0.9820 |
| 5.0 | 0.0843 | 0.6092 | 0.7870 | 0.9600 | 0.9664 | 0.9776 |
| 7.5 | 0.0245 | 0.4755 | 0.6982 | 0.9406 | 0.9501 | 0.9666 |
| 10.0 | 0.0071 | 0.3712 | 0.6194 | 0.9216 | 0.9340 | 0.9557 |

The ratio of the absorption coefficients (atomic photon cross sections) for the **167.437** of $^{201}$Tl and **439.56** of $^{202}$Tl is reduced to **0.0843** (Tab. 3, Figs. 3 and 4). It is possible in this way to count larger activities, having a sharp decrease in DT, random summation and pile-up peaks and other spurious effects. In particular, the lead shielding decreases the overall counting rate of a factor **670** (1150/1.71), in the energy range 95-335 (Fig. 4).
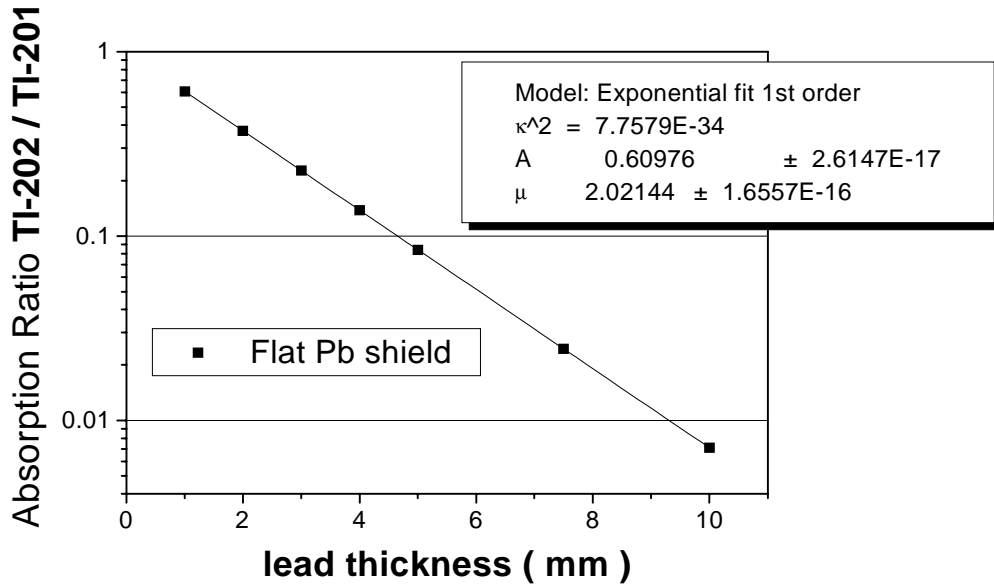


FIG. 3: Absorption ratio **R** in Pb for 167.437 keV ($^{201}$Tl) to 439.56 keV ($^{202}$Tl) gamma emissions, calculated by eq. (4).
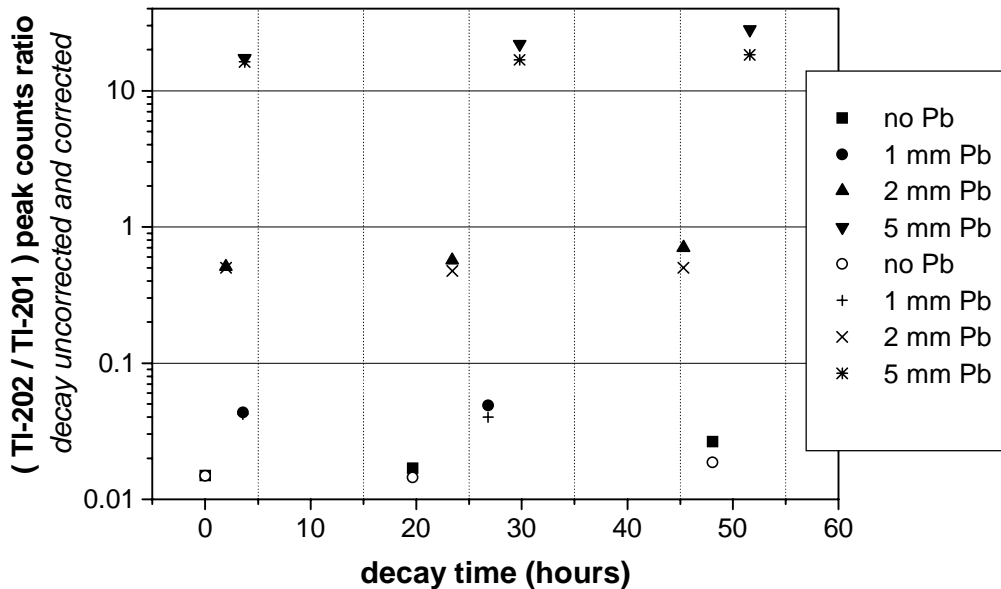


FIG. 4: Experimental ratios of net areas of **439.56** keV photo-peak of $^{202}$Tl to the **167.437** keV photo-peak of $^{201}$Tl , in a *commercial* sample of [$^{202}$Tl]-thallium (I) chloride in saline. Decay corrected (open points, lower) and uncorrected (full points, upper).
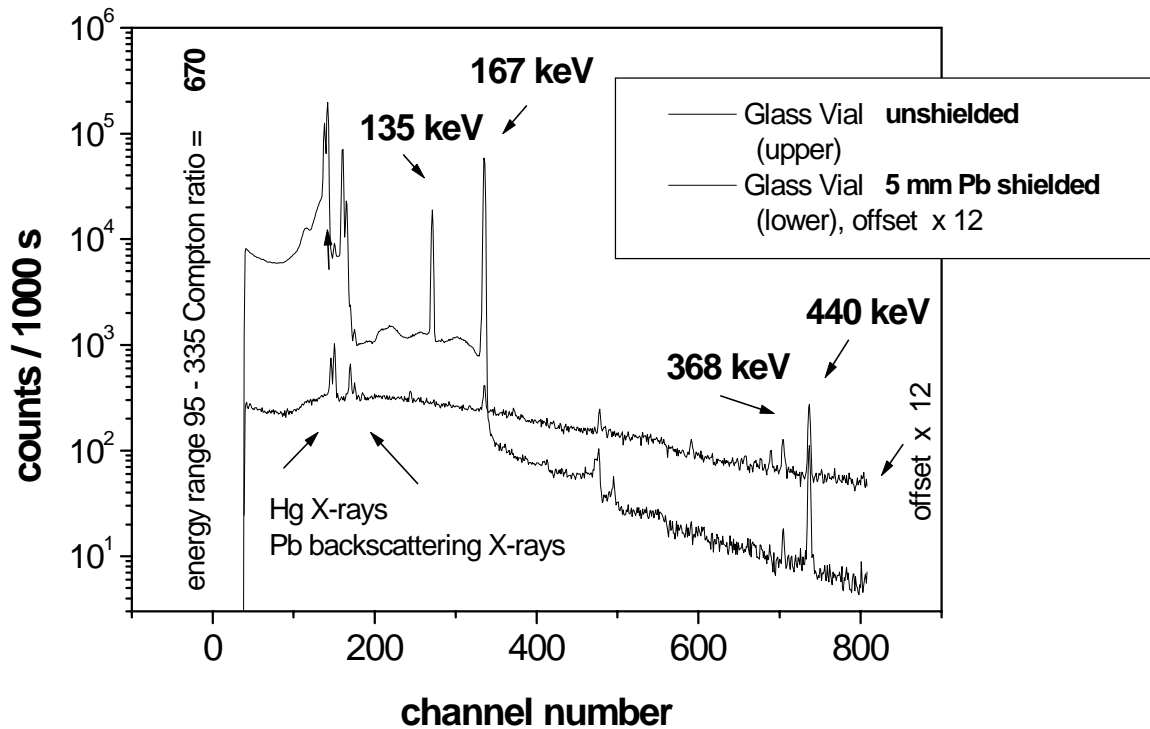
**FIG. 5**: Comparison of two γ-spectra of the **same** $^{201}$Tl sample, containing $^{200}$Tl and $^{202}$Tl impurities. The 5 mm Pb shielded spectrum is multiplied of an offset factor of 12 (only for presentation purposes). The only significant γ-peak detected in the 800 – 4096 channels range, is that due to $^{40}$K at 1460.830 keV (glass vial and natural background).

**TAB. 4**: Experimental ratios of net areas of **439.56** keV photo-peak of $^{202}$Tl to the **167.437** keV photo-peak of $^{201}$Tl in a *commercial* sample of [$^{202}$Tl]thallium(I) chloride in saline, vs. Pb thickness Dx (decay corrected to time zero, left and *uncorrected*, right).

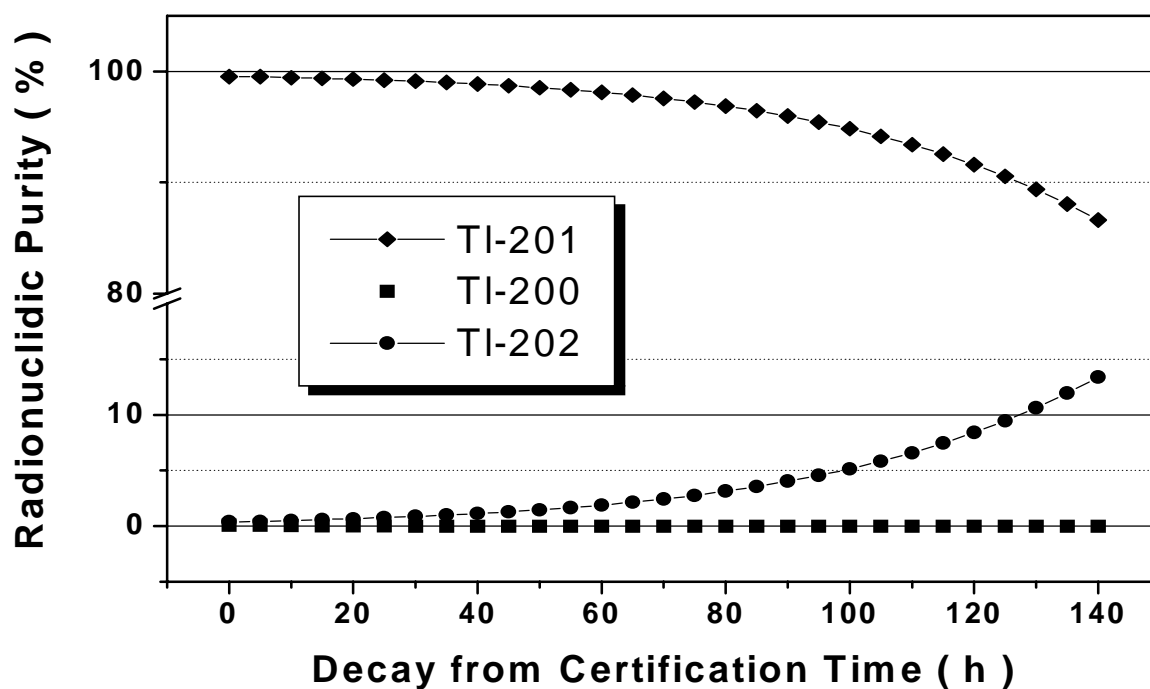| R | decay time (hours) ------> | | | | | |
|---|---|---|---|---|---|---|
| **DX (mm)** | 0.00 | | 19.65 | | 48.08 | |
| 0.0 | **1.486E-02** | *1.494E-02* | 1.451E-02 | *1.687E-02* | 1.860E-02 | *2.649E-02* |
| | 3.57 | | 26.82 | | | |
| 1.0 | **4.208E-02** | *4.330E-02* | 4.000E-02 | *4.888E-02* | | |
| | 1.98 | | 23.42 | | 45.32 | |
| 2.0 | **5.012E-01** | *5.098E-01* | 4.741E-01 | *5.661E-01* | 5.020E-01 | *7.015E-01* |
| | 3.75 | | 29.80 | | 51.58 | |
| 5.0 | **1.630E+01** | *1.724E+01* | 1.687E+01 | *2.192E+01* | 1.831E+01 | *2.807E+01* |

**FIG. 6**: Radionuclidic purity (activity %) of a commercial sample of $^{201}$Tl, vs. waiting time since the Certification Time (CT=0).
The $^{201}$Tl activity percentage reaches a value of 95.0% at 97 hours from CT.


## 10    RESULTS AND CONCLUSIONS

The shielding of [$^{201}$Tl]labelled radiopharmaceuticals, by a high Z absorber (Pb), is effective for *counting larger activities of the sample in a shorter time*, with a sharp reduction of both continuum Compton spectra of $^{201}$Tl photo-peaks, X-rays background, random summations and pile-ups.

An experimental gain on counting ratio of **20 ± 1** is obtained with a 5 mm thick Pb shielding (Fig. 5 and Tab. 4). This counting set-up, allows the accurate determination of the long-lived radioisotopic impurity $^{202}$Tl at levels of the order of 0.01%, with short counting times and acceptable counting dead times (few %).

Thus, if the only "high" energy radionuclidic impurity in $^{201}$Tl is $^{202}$Tl, it is possible to calibrate the MCA-chain for both energy and efficiency, with a *wide energy range shielded* calibration sources (i.e: either solid $^{226}$Ra or liquid $^{152}$Eu), with a sharp increase of sensitivity, lower DT and shorter counting times.

In Fig. 5 are compared two γ-spectra of the **same sample** of [$^{201}$Tl]thallium(I) chloride (Mallinckrodt Medical B.V., Ltd.) counted in both a 2 mm thick glass vial and in the same vial shielded by a cyclindrical, 5 mm thick, Pb envelope (counting chain: EG&G ORTEC, mod. 572 spectroscopy amplifier, MCB mod. 919). The activity composition of the sample at *certification time* (December 19/2000, 06.00 p.m.) was: $^{201}$Tl = 99.51 %, $^{200}$Tl = 0.0899 %,

$^{202}$Tl = 0.40 %. In accordance with the USP **24** (2000) [69] this sample expired 97 hours (1.33 $t_{1/2}$ of $^{201}$Tl) from CT (Fig. 6). Under the previous conditions it is possible to measure the radionuclidic contaminant $^{202}$Tl, even with ionisation chamber dose calibrators (like Capintec CRC-30, USA). The same method is effective in order to evaluate contamination by the short-lived $^{200}$Tl, even if in practical cases this radionuclide is present in negligible amounts (see Figs. 5 and 6).

Some preliminary results of present novel Quality Assurance method were recently presented in international meeting [80] and international journals [80,81].

The use of "low background" depleted uranium (DU) instead of lead, as shielding material, due to its higher Z and density, would be a further improvement of this quality assurance technique, by use of a thinner shielding envelope.

Finally, it is well known that, the same principle is extensively used in nuclear medicine departments, to evaluate content of $^{99}$Mo (**822.972** keV, **960.754** keV, $t_{1/2}$ = 65.94 h) break-through, coming from $^{99}$Mo/$^{99m}$Tc generators, in [$^{99m}$Tc]labelled RP compounds (**140.511** keV, 89.06%; 142.63 (weak) keV, $t_{1/2}$ = 6.01 h).

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The year 2001 is very relevant for the history of Nuclear Applied Physics, Nuclear Chemistry and Radiochemistry. It is the centennial anniversary of the Nobel Prize in Physics to Wilhelm Conrad Roentgen for the discovery of X-rays. It is the centennial anniversary of birth date of Enrico Fermi, Nobel Prize in Physics 1938. Finally, on December 20, 2001 is the 50$^{th}$ anniversary of the first production of electricity by nuclear energy, by the first Experimental fast Breeder nuclear Reactor (EBR-I) at the National Reactor Testing Station in Idaho, USA, under the supervision of Enrico Fermi, Walter Zinn and Leonard Koch.

Radionuclide production for both diagnostic and systemic radiotherapy is a recognised application of nuclear technology era, for improving health, quality of life and well-being of humanity.

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