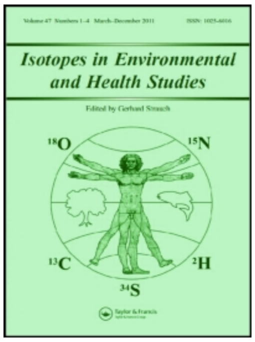

Isotopenpraxis Isotopes in Environmental and Health Studies

ISSN: 0021-1915 (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gieh19

Recent Developments and Trends in the Production of Radioisotopes in Hungary

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To cite this article: T. Lengyel , L. Szirtes & G. Tóth (1979) Recent Developments and Trends in the Production of Radioisotopes in Hungary, Isotopenpraxis Isotopes in Environmental and Health Studies, 15:10, 306-309, DOI: 10.1080/10256017908544362

To link to this article: https://doi.org/10.1080/10256017908544362

wobei

$$c_F = \sqrt{\frac{2 \cdot c_z \cdot l}{\pi}} \qquad (44)$$

angenommen wurde (c_F = Radius Kreisfläche, c_Z = Zylinderradius). Ein Vergleich mit den Rechenwerten nach geo11 in Tab. 11 zeigt, daß zur genauen Charakterisierung von experimentellen Anordnungen unbedingt auf Berechnungen gemäß geo11 bzw. Gl. (40) zurückgegriffen werden muß.

Eingegangen am 9. 5. 1979

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Recent Developments and Trends in the Production of Radioisotopes in Hungary*)

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The development of radioactive products in Hungary is discussed with special emphasis on sealed sources and radiopharmaceuticals. In case of the latter the increasing role of radioimmunoassay is stressed and the main trends in research and development are dealt with.

(D13) INIS DESCRIPTORS:

cobalt 60; Hungary; iodine 125; iridium 192; isotope production; planning; promethium 147; radioimmunoassay; radiopharmaceuticals; sealed sources; technetium 99; tritium compounds

When recalling the cautious forecasts of our previous meetings held in Paris, Belgrade, Madrid, Budapest and Athens as regards future trends and development, and comparing these with the effective achievements, the malicious phrase formulated by Dr. *Peppard* and presented as a toast on a conference-banquet seems to be verified: "No amount of planning will ever replace dumb luck!"

Turning the words more serious, four years ago at our last meeting we would not had taken the risk to forecast a 45% increase of the production volume for this period, totalling more than 21 million Forints in 1978.

First of all we would like to deal with general problems. As far as the export share is concerned, in the given period it varied between 46–58% and presently it represents 48%.

These figures refer to the production of the Institute of Isotopes only. Some radioactive products, first of all kits for radioimmunassay, some radiopharmaceuticals and sealed sources are imported. All these items are — according to inland regulations — checked and dispensed by the Institute. When comparing the total number of shipments dispatched (in 1978 totalling 15700) with that of the inland produced items a ratio of about 2 to 1 can be established. Indirectly the number of shipments reflects the overall turnover figures as well and these show a 67% increase as compared with data of 1974.

The main interests tend towards the increased use of radiopharmaceuticals and sealed sources. In the case of the former the recent years presented a jump leap of in vitro diagnostic kits while the development in the latter is characterized by the continuous spreading of the radiographic technique and, as a consequence, an increasing demand for high activity ^{192}Ir sources can be observed. In the last few years the use of radioluminescent paints and radiation excited light sources have also gained in importance.

The irradiation facilities did not change basically in the recent years and this calls forth the need for widening the circle of our cooperating partners. Regrettably, most of the reactors in the neighbouring countries have their regular shut-down in the same summer period and — an annoying foreshadow for the future — since most of these first generation research reactors were built near simultaneously, their reconstructions may be expected in the early eighties, also in the same period.

As far as accelerator irradiations are concerned, Hungary plans to put its first cyclotron into operation by 1984 only and so a shortage in home-made radioactive products is foreseen in a five years outlook. This is planned to be partly overcome by trying to arrange irradiation service in the neighbouring reac-

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*) Vortrag gehalten auf dem 6th Meeting of European Radioisotope Producers, Dresden (DDR) 23.–25. 1. 1979

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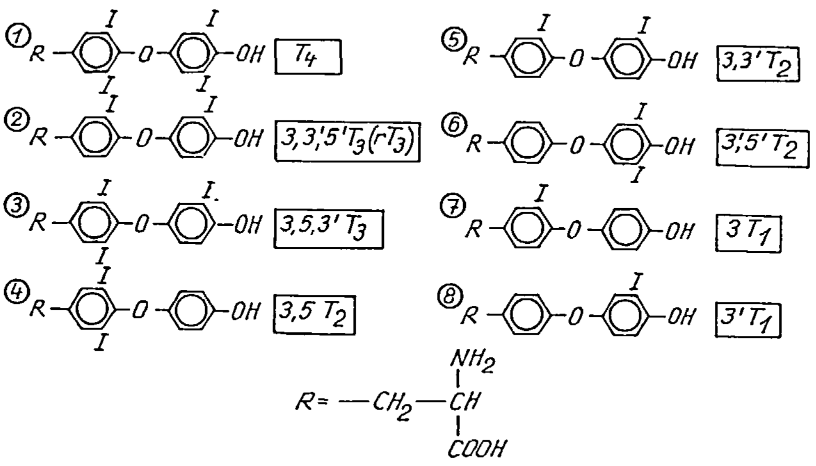

Fig. 1. Radioiodine labelled iodothyronines
Bitte beachten: in der Formel 2 steht auch in o'-Stellung zur OH-Gruppe noch ein I.

tors abroad, as far as medium or long-lived nuclides are concerned. For routinely used radiochemicals and pharmaceuticals containing short-lived isotopes the conception is to irradiate the corresponding target materials in the Training Reactor of the Technical University of Budapest, the output of which will be enlarged by a factor of ten for this period.

As far as the classification of inland customers is concerned, the medical sphere predominates, representing about 60% of the total. This is followed by the industrial users the share of which can be estimated to 25%, the rest being the contribution of the research and agricultural fields.

After this general review further on we would like to deal with the most important results which were attained since our meeting in Athens.

After having realized our so-called "Instant Technetium Programme", according to which the inland customers in the Budapest area are supplied daily with ^{99m}Tc in the form of sterile isotonic sodium pertechneeate solution, three in vivo kits were worked out to facilitate rapid diagnostic assay. These render possible to prepare instantly the corresponding citrate, phosphonate and phytate compounds which in turn can advantageously be used for imaging the function of the kidneys, detection of skeletal diseases and the reticulo-endothelial system (RES), respectively. In order to facilitate proper dosaging, simulating reference sources containing ^{141}Ce are also supplied.

The production of tritium-labelled prostaglandins represents another dynamically developing field. These are prepared on biochemical basis, making use of the proper enzyme-system from tritium-labelled arachidonic acid. The purification is performed with the aid of preparative thin layer chromatography [1].

At present the E_2, $F_{2\alpha}$, A_2 and B_2 prostaglandins are regularly produced with a specific activity of about 4 TBq/mmole.

The most recent result in this field is that we succeeded in the preparation of the ^{125}I-labelled thyrosin methylester derivative of $F_{2\alpha}$ prostaglandin, which, in our opinion, presents new vistas as regards prostaglandin radioimmunassay.

In addition, in the scope of our development programme the production of six radioiodine labelled iodothyronines (out of the existing eight shown in Fig. 1) was performed. In the case of ^{125}I-labelled triiodothyronine and thyroxine we aimed at rendering the competitive protein binding and radioimmunassay of thyroid hormones in the clinical laboratories possible, while ^{125}I-labelled reverse triiodothyronine, diiodothyronines and 3' iodothyronines were considered as being important aids in the thyroid hormone metabolic studies.

The well-known "chloramin T" method was used to labell the iodothyronines mentioned. The feature of this labelling procedure is that it leads to the formation of labelled by-products, partly due to the homogeneous isotopic exchange taking place at the 3' and/or 5' positions, simultaneously with the electrophilic substitution, and partly due to the oxidizing effect of the chloramine T. By the way this is why the after-labelling purification of the radioiodothyronine of interest can not be omitted.

The adsorption chromatographic separation of iodothyronine pairs (e.g. triiodothyronine and thyroxine) is usually based on the finding that Sephadex-type dextrane gels like G-25 and LH-20 reversibly adsorb organic acids in non-ionized form, while dissociation of the carboxyl or phenolic hydroxyl group results in the decrease of the adsorption affinity and thus in the decrease of the distribution coefficient as well.

Segregation of two or more organic acids, e.g. iodothyronines, by adsorption chromatography seems to be possible only when a considerable difference in the pK values exists (pK represents the pH value at which 50% of the phenolic hydroxyl group is dissociated).

From the data of Tab. 1. the conclusion can be drawn that the eight iodothyronines form three groups with regard of the pK_{OH} values only, which is due to the fact that the acidity of the phenolic hydroxyl group is influenced by the number or iodine substituents at the 3' and/or 5' positions, irrespectively of the number of iodine atoms at the 3 and/or 5 positions.

In order to overcome the difficulties arising from the very close pK_{OH} values of several iodothyronines, it was aimed at

Tab. 1. Classification of iodothyronines according to the number of iodine atoms per molecule and to the number of iodine atoms in the molecule

Number of iodine atoms per molecule	in the phenolic ring		
	0	1	2
1	3T1	3'T1	
2	3,5T2	3,3'T2	3',5'T2
3		3,3'5T3	3,3'5T3 (rT3)
4			T4
pK_{OH}	9.3–9.5	8.3–8.5	6.4–6.7

developing a separation method based on the different adsorption affinities of iodothyronines towards the dextran gel as a function of the number of iodine atoms per molecule, instead of the different adsorption affinity as a function of the ionized or non-ionized state of the phenolic hydroxyl group.

It was revealed that at *p*H less than 4, i.e. where the phenolic hydroxyls of iodothyronines are non-ionized, the adsorption affinity and thus also the elution volume increases with increasing number of iodine atoms per molecule, irrespectively of their positions [2].

On the other hand, it has also been shown that organic solvents compete with iodothyronines for the surface sites of the dextran gel: the higher the organic solvent concentration of the eluent, the smaller elution volume and distribution coefficient can be achieved.

In Fig. 2 representative elution patterns obtained with binary eluents containing 50, 40 and 30% aqueous ethanol for separation of T3 and T4 are shown. Fig. 3. demonstrates that there exists a linear relationship between the logarithms of the distribution coefficients and the solvent concentration which renders possible the systematic adjustment of the distribution coefficient required by choosing the proper solvent concentration.

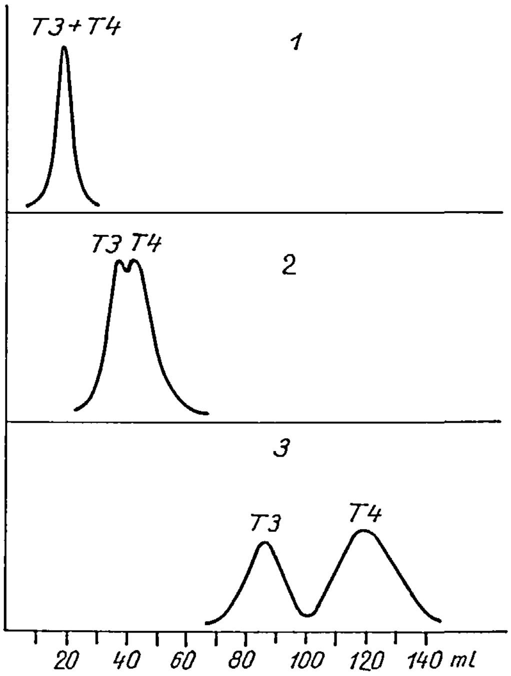

Fig. 2. Elution curves ovbtained by the chromatography of T3 and T4
Curve 1: Eluent 50 vol% ethanol, *p*H = 4; Curve 2: Eluent 40 vol% ethanol, *p*H = 4; Curve 3: Eluent 30 vol% ethanol, *p*H = 4

Since the slopes of the log *k* vs. log (*S*) straight lines are different for iodothyronines with different number of iodine atoms per molecule, it goes without saying that, besides the distribution coefficient values the selectivity of the separation, defined for two adjacent bands as the ratio of the *k*-values, can be controlled by the solvent concentration as well. In Fig. 4. the selectivity of the separation of *r*T3 and 3,3′T2 as a function of the ethanol concentration of the eluent is shown [3, 4].

In order to facilitate routine diagnostic work, for the determination of insulin resistance of patients, i.e. for the assay of insulin-binding antibodies in sera a kit containing ^{125}I-labelled insulin has also been developed. The separation of the bound and unbound tracer is performed with polyethylene glycol.

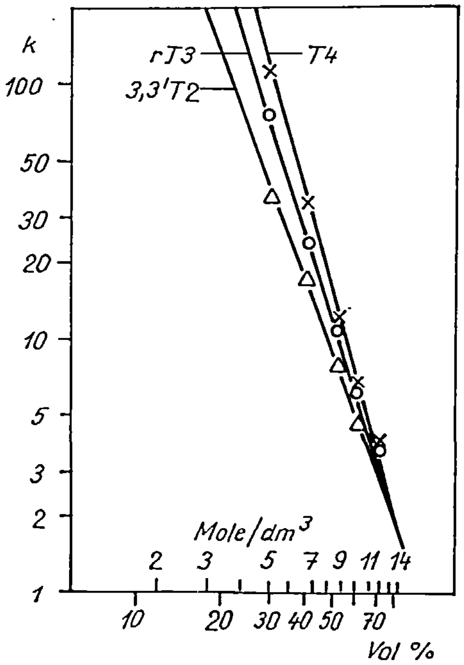

Fig. 3. The distribution coefficient (*k*) vs. solvent concentration (*S*) shown in log-log plot

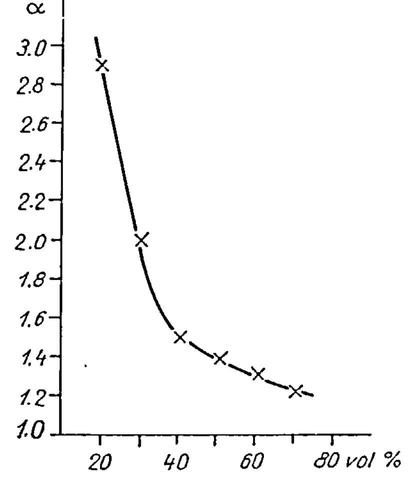

Fig. 4. The dependence of the selectivity coefficient on the ethanol concentration of the eluent for the separation of *r*T3 and 3,3′ T2

Finally we would like to give a review on the development in the field of sealed sources.

Among the sources used in therapeutic work the production of ^{60}Co spheres represents a new step [5]. These spheres of 3·2 mm diameter and 400 MBq activity are used in the so-called "afterloading technique" and the main feature of their production is that they are prepared as sealed sources by welding the stainless steel coverage and maintaining a non-deformed globular shape. This latter is achieved by a finishing procedure performed in a device like a ball-grinder.

The increasing demand for high activity ^{192}Ir sources made indispensable to utilize reactor irradiation service abroad. This rendered possible to content the inland customers with ^{192}Ir sources of 5 TBq activity with active dimensions of 3 × 3 mm.

A special source for radioagraphy of plastic sheets and tubes was also constructed. It contains up to 1 TBq of ^{147}Pm and the bremsstrahlung from a zirconium oxide target at an energy range 15—20 keV is utilized.

One of the most spectacular development can be observed in the production of light sources. The different luminescent paints (activated zinc or cadmium sulphide) are excited by the soft β-radiation of ^{147}Pm. The main feature is that using standard discs of 1 cm^2 surface optional forms and shapes can be prepared. The most common one has a lighting surface of 100 cm^2, containing 37 standard discs in symmetric arrangement and comprising near 80 GBq ^{147}Pm.

The bremsstrahlung is shielded by lead, the stainless steel holder is welded and the front cover is prepared from lead glass. As a result of the carefully developed technology the dose rate at the surface of the source does not exceed 70 pA/kg and the whole assembly suits the specifications for the second category sealed sources, according to the ISO regulations.

In summarizing the results of the last four years, as far as Hungary is concerned, a steady progress has continued which allows optimistic forecasts for the future.

Received April 11, 1979

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Isotopenverdünnungsanalyse mit der Funkenquellen-Massenspektrometrie

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Es wird über Untersuchungen zur massenspektrometrischen Isotopenverdünnungsanalyse mit stabilen Nukliden unter Verwendung von Hochfrequenzfunken-Ionenquellen berichtet. Die Analysenmethode zeichnet sich durch eine gute Richtigkeit und Reproduzierbarkeit der Analysenergebnisse mit durchschnittlichen Standardabweichungen von 5% bis 10% im ppm-Bereich aus. Durch die Anwendung des elektrischen Ionennachweises und der Ionenstromverstärkung mittels Sekundärionenvervielfacher konnten die Analysenzeiten gegen über der Isotopenverdünnungsanalyse mit photographischer Ionenstromregistrierung wesentlich gesenkt werden.

(B11) INIS DESCRIPTORS:

accuracy; copper 63; copper 65; electron multipliers; graphit; ion detection; isotope dilution; isotope ratio; mass spectroscopy; quantitative chemical anaysis; spark mass spectrometers; strontium; trace amounts

1. Einleitung

In einer früheren Arbeit [1] wurde über die Methodik und die Ergebnisse eines Analysenverfahrens zur isotopenverdünnungsanalytischen Multielementanalyse mit der Funkenquellen-Massenspektrographie berichtet. Dieses Analysenverfahren zeichnet sich durch eine hohe Richtigkeit und eine gute Präzision der Meßergebnisse aus, wobei das Nachweisvermögen mit Nachweisgrenzen bis in den ppb-Bereich hoch ist. Dazu trägt unzweifelhaft der photographische Ionennachweis bei, der durch seine extreme Empfindlichkeit und sein Integrationsvermögen bei gleichzeitiger Registrierung aller Ionenströme einen idealen Datenspeicher hoher Speicherkapazität darstellt. Ein Nachteil der photographischen Registrierung der Ionenströme ist, daß die Rückgewinnung der Analyseninformationen durch den Entwicklungsprozeß der Photoplatten und deren photometrische Auswertung u. U. zeitraubend ist. Deshalb scheint es zweckmäßig zu untersuchen, inwieweit eine schnellere Analyse durch den Einsatz der elektrischen Registrierung der Ionenströme aus einer Funkenionenquelle erreicht werden kann. In einer Reihe von Arbeiten zum elektrischen Ionennachweis von Ionenströmen aus Funkenionenquellen konnte gezeigt werden, daß Analysenergebnisse mit vergleichbaren Nachweisgrenzen wie mit dem photographischen Ionennachweis, aber vergleichsweise niedrigeren Standardabweichungen erzielt werden [2—4]. Ein wesentlicher Vorteil des elektrischen Ionennachweises ist die unkomplizierte und damit schnellere Auswertung der Massenspektren, die u. U. sogar mit einer on-line-Kopplung des Massenspektrometers mit einem Computer durchgeführt werden kann. Ein Nachteil für den elektrischen Ionennachweis sind die stark schwankenden Ionenströme, die aus einer Funkenionenquelle extrahiert werden.

In dieser Arbeit soll über Untersuchungen zur Möglichkeit einer massenspektrometrischen Isotopenverdünnungsanalyse mit stabilen Tracern unter Verwendung einer Hochfrequenzfunken-Ionenquelle berichtet und an Hand der Meßergebnisse an geologischen Standardproben sollen die Vorteile und Grenzen des Analysenverfahrens diskutiert werden.

2. Instrumentelles

Als Probenmaterial wurden geologische Standardproben des Zentralen Geologischen Instituts Berlin verwendet [5]. Das nichtleitende feingemahlene Probenmaterial wurde mit Reinstgraphit (RWS, Ringsdorf-Werke, BRD), dem vorher der stabile Tracer zugegeben worden war, gemischt, homogenisiert und zu Elektroden gepreßt, die in die Hochfrequenzfunken-Ionenquelle eines doppelfokussierenden Massenspektrometers eingebaut wurden. Einzelheiten zur Probenpräparation, zur Isotopenverdünnungsanalyse und zur Herstellung des Tracer-Graphit-Gemisches können [6, 1] entnommen werden. Für die Untersuchungen standen zwei doppelfokussierende Massenspektrometer vom *Mauttauch-Herzog*-Typ zur Verfügung: das Massenspektrometer MS 702 R (AEI, England) und das Massenspektrometer MX 3301 (SKB Leningrad, UdSSR). Der Ionennachweis erfolgt bei beiden Geräten mit offenen SEV-Systemen, wobei das MS 702 R mit einem 20stufigen SEV (Kupfer-Beryllium-Dynoden) und das MX 3301 mit einem SEV-System mit kontinuierlichen Dynoden ausgestattet ist. Zur elektrischen Ionen-

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