Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 312–317.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1203

JLCR

Short Research Article

IAEA activities in support of production and utilization of radioisotope labelled compounds†

NATESAN RAMAMOORTHY*, MAROOR RAGHAVAN AMBIKALMAJAN PILLAI, JOON-HA JIN and SEYED MOHAMMAD HAJI-SAEID

Division of Physical and Chemical Sciences (NAPC), Department of Nuclear Sciences and Applications (NA), International Atomic Energy Agency (IAEA), A-1400 Vienna, Austria

Received 24 August 2006; Revised 22 November 2006; Accepted 23 November 2006

Abstract: The development of a large variety of radioisotope labelled compounds as well as the ability to design and prepare specific products forms the basis for several important applications in medicine, industry and research. As a part of the IAEA's role in fostering the peaceful uses of nuclear science and technology, the IAEA's Division of Physical and Chemical Sciences has focused attention on the important classes of compounds such as, fluorine-18 products; technetium-99m labelled complexes; products for radionuclide therapy of yttrium-90, samarium-153, lutetium-177 and rhenium-186/188; industrial radiotracers based on bromine-82 labelled compounds, tritiated water and carbon-14 labelled thiocyanate. A number of coordinated research projects (CRP) and technical cooperation projects have been implemented for this purpose. Thematic technical and consultancy meetings have been held to review the status and prepare technical documents on specific topics of interest for developing Member States (MS). These measures have contributed to several developing MS acquiring/enhancing expertise in building local facilities and capability in the production and utilization of radioisotope labelled compounds. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: radioisotope; labelled; radiopharmaceutical; radiotracer

Introduction

The IAEA has been helping the developing Member States (MS) during the last several decades towards capacity building for local production of radioisotopes and for cost effective and large scale applications in nuclear medicine. Owing to the Agency programs in the above areas, several member states have successfully built radioisotope programs catering to the local needs of radiopharmaceuticals including ^{99m}Tc generators, cold kits and cyclotron based SPECT and PET radiopharmaceuticals.

Radiotracers have been widely used throughout the industry to optimize processes, trouble-shooting, improve product quality, save energy and reduce pollution. Their technical, economical and environmental benefits have been well demonstrated and recognized by the industrial and environmental sectors. The Agency has helped interested developing MS in this area by supporting development, production and utilization of industrial radiotracers.

A number of coordinated research projects (CRP) and technical cooperation (TC) projects have been implemented for the above purpose. Thematic technical and consultancy meetings have been held to review the status and prepare technical documents on specific topics of interest for developing MS. This paper covers the highlights of such activities implemented recently by the IAEA for the benefit of developing MS.

Radioisotope labelled compounds for application in medicine

The success of the completed CRP in the area of radiopharmaceuticals is based on many countries

*Correspondence to: Natesan Ramamoorthy, Division of Physical and Chemical Sciences (NAPC), Department of Nuclear Sciences and Applications (NA), International Atomic Energy Agency (IAEA), A-1400 Vienna, Austria. E-mail: n.ramamoorthy@iaea.com

†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.

willingness to share their core competencies and complementary skills and this has helped in carrying out many need-based development activities. This has later led to the use of the products for clinical applications. The Agency run CRPs have helped in regional and interregional networking of scientists to develop and/or improve the quality of locally made products. The results of the research projects are compiled in the form of Agency publications and can be freely downloaded.[1–7] Many of the CRPs also resulted in demands for further capacity building through national TC projects.

CRP on 'Comparative Laboratory Evaluation of Therapeutic Radiopharmaceuticals'

The CRP on 'Comparative Laboratory Evaluation of Therapeutic Radiopharmaceuticals' was concluded in November 2005. The major achievements of the CRP include the development of peptide based radiopharmaceuticals labelled with the therapeutic radionuclides, ^{177}Lu and ^{131}I. Some of the participants produced ^{177}Lu as a therapeutic isotope in adequately high specific activity (>185 GBq/mg) and radionuclidic purity required for radiolabelling of peptides. The CRP helped in the development of several protocols for radiolabelling procedures for peptide and other high specific activity tracers for targeting low capacity systems. Protocols for carrying out biological evaluations in particular, for tissue culture, cell binding and animal bio-distribution studies have been developed and implemented. Most of the participants have demonstrated the use of specialized animal handling facility for studies of therapeutic radiopharmaceuticals, since the studies have been carried out in xenografted tumour-bearing nude mice. Techniques to study radiobiological effects of different regimens of targeted radionuclide therapy have been developed. Through the CRP, the participants have acquired the skill of working with small quantities of biologically active molecules and optimized their use towards carrying out different assays. The major achievement of the CRP is the development of a protocol for the preparation of ^{177}Lu-DOTATATE for targeted therapy of neuro-endocrine tumours.

CRP on 'Development of ^{99m}Tc Based Small Bio Molecules Using Novel ^{99m}Tc Cores'

^{99m}Tc radiopharmaceuticals are used in about 80% of the current nuclear medicine services and are also a powerful tool for nuclear medicine studies in the developing World. The earlier CRPs, TC projects and related program have helped in building capacity for production of established radiopharmaceutical products for static and dynamic studies. The CRP on 'Development of ^{99m}Tc Based Small Bio Molecules Using Novel ^{99m}Tc Cores', started during 2003, with an overall objective to generate know-how and expertise in participating laboratories for applying the recent advances in ^{99m}Tc chemistry such as the ^{99m}Tc tricarbonyl and ^{99m}Tc nitrido chemical approaches for ^{99m}Tc labelling of small biomolecules. Owing to this CRP, the fundamental chemical methods required for the preparation of the different ^{99m}Tc cores (carbonyl, hynic, nitrido, and mixed ligand) were efficiently transferred to the various laboratories involved in the CRP. Participants worked with RGD peptides, Annexin derivatives, fatty acid derivatives for radiolabelling studies. Some promising ^{99m}Tc labelled biomoleucles with RGD and Annexin analog peptides developed during the CRP are deemed worth pursuing further for possible clinical use.

Support to strengthening MS capacity in radiopharmaceuticals production

The IAEA has been helping the MS in the last several decades to build capacity for local production of radiopharmaceuticals for cost effective and large scale applications in nuclear medicine. Thanks to the Agency support in the above areas, several member states have successfully built radioisotope programs catering to the local needs of radiopharmaceuticals including ^{99m}Tc generators, cold kits, cyclotron based SPECT and PET radiopharmaceuticals. The strengthened capacity in radiopharmaceuticals has significantly contributed towards increasing the nuclear medicine services available in MS, thereby improving the benefits to patients.

Through a regional project (ARCAL) in the Latin American region, the participants achieved competence in the preparation of radiopharmaceuticals based on monoclonal antibodies and peptides. Protocols for the production, quality control and validation of a few radiopharmaceuticals were developed as part of the project. The products include, ^{188}Re-anti CD20, ^{131}I-anti CD20, ^{188}Re-anti-egf/r3, ^{99m}Tc anti-egf/r3, ^{99m}Tc-anti-CEA, ^{99m}Tc-hynicTOC, ^{99m}Tc-Ubiquicidine 29-41 (UBI). A few of the participating countries, which had collaboration with nuclear medicine departments, reported the use of the diagnostic radiopharmaceuticals in patients (^{99m}Tc-HynicTOC and UBI). Through regional projects in Asia and Pacific, the IAEA has helped the MS in enhancing the MS capability for compliance with codes of GMP. This program is now being expanded to include several more interested countries.

DOI: 10.1002.jlcr

Table 1 ^{18}F radiopharmaceuticals

Oncological applications
[^{18}F]fluoro choline, [^{18}F]FLT: 3′-Deoxy-3-[^{18}F]fluorothymidine, [^{18}F]FDOPA: 6-[^{18}F]fluoro_L-DOPA, [^{18}F]FET: *O*-(2′-[^{18}F]fluoroethyl)-L-tyrosine (FET), [^{18}F]PFBG: *Para*-[^{18}F]fluoro benzylguanidine, [^{18}F]F-Misonidazole, [^{18}F]F-FAZA, [^{18}F]Fluoro-etanidazole, 7 α -[^{18}F]F-MDHT: [7α-^{18}F]fluoro-17 α –methyl-5 α –dihydrotestosterone (Dihydro testosterone derivatives), [^{18}F]FES: [^{18}F]fluoro-17β-estradiol, [^{18}F]NaF, ^{18}F-labelled monoclonal antibodies, fragments and peptides
Neurology application
[^{18}F]FDOPA: 6-[^{18}F]fluoro-L-DOPA, [^{18}F]Fallypride, [^{18}F]MPPF, [^{18}F]Fluoroethyl spiperone
Cardiac tracers
[^{18}F]Fluoro-Fatty acids and fluoropalmitate, [^{18}F]PFBG: *para*-[^{18}F]fluorobenzylguanidine, 4- and 6-[^{18}F]fluorometaraminol
Reporter gene imaging
[^{18}F]FHBG: 9-[(3-[^{18}F]-fluoro-1-hydroxy-2-benzo) methyl guanine, [^{18}F]FHPG: 9-[(3-[^{18}F]-fluoro-1-hydroxy-2-propoxy) methyl guanine

Consultancy Meeting on 'Advances in the Preparation and Quality Control Techniques for ^{18}F labelled radiopharmaceuticals'

A number of MS are in the process or planning to set up medical cyclotron, radiochemistry and PET imaging facilities. Their major emphasis is on the use of [^{18}F]FDG for clinical applications. However, these centers also have scope for developing other clinically important ^{18}F radiopharmaceuticals as well as radiopharmaceuticals based on other PET isotopes as the cyclotron and the radiochemistry laboratory will be used only for a part of the time for the routine production of [^{18}F]FDG. The Consultancy Meeting convened to address important issues involved in the preparation and application of ^{18}F labelled radiopharmaceuticals, reviewed the development of new ^{18}F PET tracers. In general, there is more emphasis on specific radiotracers for oncology applications and on several new radiotracers useful in neurology and cardiac applications. Among the compounds discussed, the ones identified as of high potential are listed in Table 1. The IAEA proposes to initiate coordinated research for the development and technology transfer of some of the most useful ^{18}F tracers.

Support to major meetings for facilitating information exchange on current advances in radiopharmaceuticals

The IAEA extends cooperation support to major meetings in the areas of radioisotopes and radiopharmaceuticals to facilitate participation of young scientists from developing MS associated with the IAEA activities to benefit by interactions with researchers from developed countries. Effective collaborations and partnerships are developed and several success case studies are citable. In addition, the IAEA itself has organised a number of Symposia in this field,[8–9] with the International Symposium on Trends in Radiopharmaceuticals- ISTR 2005 held during 14–18 November 2005 being the most recent one. The ISTR-2005 addressed important developments in the design, production, evaluation and application of radiopharmaceuticals. Two hundered and twenty participants and 17 observers from 71 Agency Member States attended the Symposium. One hundred and forty nine papers from 51 MS were presented covering various aspects of radiopharmaceutical sciences, in addition to 22 invited talks which covered the important advances and trends. The Symposium was held with representation from some of the major professional bodies in this field, namely, the European Association of Nuclear Medicine; the Society of Nuclear Medicine; the Society for Radiopharmaceutical Sciences, and the World Federation of Nuclear Medicine and Biology. The Symposium had an extensive and balanced scientific programme, including the chemistry and technology of medical radionuclides production and radiolabelling; structure–activity relation assessments; pre-clinical evaluation; clinical applications for both diagnostic and therapeutic purposes; reports on indigenous capacity built-up in production, and utilisation of radiopharmaceuticals in Member States, together with panel discussions on 'Medical Cyclotron - PET Facility' and 'GMP and Regulatory Issues'.

Radioisotope labelled compounds for tracer applications in industry and environment

The industrial radiotracer technology is today applied by developed countries as routine procedures. Many developing countries have also gathered considerable technical knowledge and experience to apply this technology to their local industry, but still there are many who are lagging behind. Various problems faced by the developing countries are non-availability of radioisotope production facilities, lack of equipment and practical knowledge for field experiments, etc. Poor

DOI: 10.1002.jlcr

Table 2 Commonly used gaseous radioactive tracers

Radionuclide	Half-life	Gamma radiation (MeV)	Chemical form
^{41}Ar	110 m	1.29 (99%)	Gas
^{79}Kr	34 h	0.261, 0.398, 0.686	Gas
^{85}Kr	10.6 y	0.514 (0.41%)	Gas
^{76}As	26.5 h	0.55 (43%)	AsH_3
^{82}Br	36 h	0.55 (70%), 1.32 (27%)	CH_3Br

Table 3 Commonly used radioactive tracers in aqueous solutions

Radionuclide	Half-life	Gamma radiation (MeV)	Chemical form
^{131}I	8.04 d	0.36 (80 %), 0.64 (9%)	NaI, KI
^{82}Br	36 h	0.55 (70%), 1.32 (27%)	NH_4 Br
^{140}La	40 h	0.33-2.54	$La(CH_3\ COO)_3$, La-EDTA
^{198}Au	2.7 d	0.41 (99%)	$HAuCl_4$
^{46}Sc	84 d	0.89 (100%), 1.48 (100%)	Sc-EDTA
^{51}Cr	27.8 d	0.325 (9%)	Cr-EDTA
^{60}Co	5.3 y	1.17 (100%), 1.33 (100%)	$[Co(CN)_6]^{-3}$

Table 4 Common industrial liquid radiotracers for organic media

Radionuclide	Half-life	Gamma radiation (MeV)	Chemical form
^{131}I	8.04 d	0.36 (80 %), 0.64 (9%)	Iodobenzene ($C_6H_5\,^{131}I$), Iodokerosene
^{82}Br	36 h	0.55 (70%), 1.32 (27%)	Paradibromobenzene ($C_6H_4^{82}Br_2$), Bromododecane ($C_{12}H_{25}\,^{82}Br$), Bromonaphthol ($^{82}BrC_{10}H_6OH$)
^{140}La	40 h	0.33-2.54	Lanthanium naphthenate
^{113m}In	100 m	0.392 (64%)	Indium oleate, Indium stearate

availability of suitable radiotracer is the greatest barrier to the use of industrial radiotracer techniques.

It is important to ensure that the radiotracer has a suitable half-life and radiations of proper energies consistent with the features of the system to be studied. In addition to this, it is of fundamental importance that the tracer compound should behave in the same way as the material to be investigated. The selection of an appropriate radioisotope labelled compound as a tracer is crucial to the success of a radiotracer study. As the traced materials and tracing circumstances are widely different, the requirements on the characteristics of the radiotracer compounds vary accordingly. Radioisotope labelled compounds are produced in gaseous, aqueous, organic or solid forms.[10]

Gaseous tracers: Some gas tracers can be produced by direct neutron activation in nuclear reactors such as ^{41}Ar and ^{79}Kr. Methyl bromide (CH_3Br) is produced through synthesis starting with radioactive ^{82}Br. Some of the commonly used gaseous radioactive tracers are given in Table 2.

Aqueous tracer: Tritiated water (HTO) is the only intrinsic radiotracer for water. Other tracers most commonly used in aqueous solutions are anions of radioisotopes and complexes labelled with cationic radioisotopes as listed in Table 3.

Organic tracers: The only intrinsic radionuclides for organic materials are ^{3}H, ^{14}C, ^{32}P and ^{35}S labelled compounds. Extrinsic tracers as listed in Table 4 are more widely used. A majority of these radiotracer compounds are obtained by labelling with radioisotopes.

Solid tracer: A common method for labelling of a solid material is direct activation i.e., to irradiate a portion of the traced material in a neutron flux and induce the necessary activities. Table 5 gives examples of widely used tracers labelled by direct activation of solids.

Adsorption or ion exchange properties of a radioisotope on the surface of a solid are used as surface labelling methods for sand particles and many powdered materials.

Some of the achievements through CRPs and technical meetings in the area of industrial applications of radiotracer compounds are discussed below.

DOI: 10.1002.jlcr

Table 5 Some radioactive tracers induced by direct activation of solids

Irradiated material	Induced radionuclides
Coal	^{46}Sc, ^{59}Fe (after decay of ^{56}Mn, ^{24}Na)
Clinker, cement	^{24}Na
Cracking catalyst	^{140}La
Gold ore	^{198}Au, ^{59}Fe, ^{42}K, ^{140}La, ^{56}Mn, ^{24}Na, ^{46}Sc,^{51}Cr
Copper ore	^{64}Cu, ^{42}K, ^{140}La, ^{24}Na
Carbon black	^{24}Na

CRP on 'Validation of Tracers and Software for Inter-well Investigations'

Inter-well tracer test is an important tool for secondary and tertiary recovery of oil and operation of geothermal plants. The main purpose of the test in oil and geothermal reservoirs is to monitor qualitatively and quantitatively the fluid connections between injection and production wells and to map the flow field. Tracer is added into injection fluid via an injection well and observed in the surrounding production wells. Tracer response is then used to describe the flow pattern and obtain better understanding of the reservoir. The CRP aims to further develop and refine radiotracer methodology for oil reservoir evaluation: to prepare, test and validate new tracers, analysis and field operation techniques, as well as to improve interpretation of tracer data.

As networking activities, the participants are taking part in inter-comparison for evaluation of their analytical capabilities as well as their understanding for result interpretation. Tritium labeled water samples were distributed in order to determine the activity concentration, error and confidence level of the measurement. Tracer production data were distributed in order to calculate breakthrough and mean resident times, swept volume, fraction of injection water reaching each well and flow paths.

Consultancy Meeting on Radiotracers and Labelling Compounds for Applications in Industry and Environment

The Meeting concentrated on the preparation of a technical report on state-of-the-art information and guidelines in radiotracer selection, preparation, validation and quality control of radiotracer methods in industry. In more detail, the report:

— suggests a method for categorization of tracers according to their defined ideal properties;
— suggests possible radiotracers for various tracing tasks;
— outlines production and preparation methods for various radiotracers;
— describes possible radiotracer behaviour with focus on limitations;
— describes procedures for preparation of tracer experiments;
— argues for increased effort related to development of suitable new radionuclide generators.

The intention is that this document will be utilized by tracer groups for planning and performing radiotracer experiments in industry and the environment.

Consultancy Meeting on Radionuclide Generators for Industrial Radiotracer Technology

For further development of tracer technology and expansion of its application in industry and environment, it is vitally important to improve the availability of tracers. A partial solution may be to develop radionuclide generators suitable for industrial use. For a radionuclide generator to be suitable for industrial use, several criteria need to be satisfied. These include half-life of the parent and daughter radionuclide, type and energy of radiation, availability and cost, etc.

The meeting evaluated the status of the radionuclide generators to identify potentially useful nuclear genetic relationships, which may form the basis for development of industrial radionuclide generators. The meeting found that some nuclear genetic relationships, such as ^{68}Ge/^{68}Ga, ^{137}Cs/^{137m}Ba, ^{144}Ce/^{144}Pr and ^{172}Hf/^{172}Lu, are suitable to produce tracers on site for industrial use. The meeting suggested creating and organizing worldwide common demands on a few kinds of suitable radionuclide generators through the cooperative work of the international radiotracer community in selecting, validating and ordering the generators. A CRP on evaluation and validation of radionuclide generator based radioisotopes and labelled compounds was proposed to enhance the availability of the industrial radionuclide generators for developing countries.

Conclusion

The IAEA will continue to support developing MS in their pursuit for benefiting from the production and

DOI: 10.1002.jlcr

utilization of radioisotopically labelled compounds for application in health sciences and industrial processes. The Agency activities will be guided by the principles of supporting need based development of products and techniques as well as the basis for technology transfer to developing MS being related to their national development plans/ initiatives.

REFERENCES

1. IAEA. *IAEA TECDOC-805*, 1995. http://nelib-w1/lib/Tecdocs/0805.pdf [November 2006].
2. IAEA. *IAEA TECDOC-1214*, 2001. http://www-pub.iaea.org/MTCD/publications/PDF/te_1214_prn.pdf [November 2006].
3. IAEA. *IAEA TECDOC-1310*, 2002. http://www-pub.iaea.org/MTCD/publications/PDF/te_1310_web.pdf [November 2006].
4. IAEA. *IAEA TECDOC-1359*, 2003. http://www-pub.iaea.org/MTCD/publications/PDF/te_1359_web.pdf [November 2006].
5. IAEA. *IAEA Technical Report Series No. 426*, 2004. http://www-pub.iaea.org/MTCD/publications/PDF/TRS426_web.pdf [November 2006].
6. IAEA. *IAEA TECDOC-1414*, 2004. http://www-pub .iaea.org/MTCD/publications/PDF/te_1414_web.pdf [November 2006].
7. IAEA. *IAEA TECDOC-1430*, 2004. http://www-pub.iaea.org/MTCD/publications/PDF/te_1430_web.pdf [November 2006].
8. IAEA. *IAEA TECDOC–1029*, 1998. http://www-pub.iaea.org/MTCD/publications/PDF/te_1029_prn.pdf [November 2006].
9. IAEA. *IAEA TECDOC-1228*, 2001. http://www-pub.iaea.org/MTCD/publications/PDF/te_1228_prn.pdf [November 2006].
10. IAEA. *IAEA Technical Report Series No. 316*, 1990.