Association of Imaging Producers and Equipment Suppliers
European Industrial Association for Nuclear Medicine and Molecular Healthcare

Report on Molybdenum 99 Production for Nuclear Medicine 2010 - 2020

State of the Art

REPORT ON MOLYBDENUM-99 PRODUCTION FOR NUCLEAR MEDICINE – 2010 – 2020

Association of Imaging Producers & Equipment Suppliers
(European Industrial Association for Nuclear Medicine and Molecular Healthcare)

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REPORT ON MOLYBDENUM-99 PRODUCTION FOR NUCLEAR MEDICINE – 2010 – 2020

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Executive Summary

The radionuclides supply for nuclear medicine is crucially dependent on an **unsustainably low number of production reactors and processing facilities** in Europe, North America, South-Africa and Asia/Pacific. Worldwide, only five (5) reactors are able to produce radionuclides on an industrial scale for medical purposes: NRU in Canada, HFR in The Netherlands, SAFARI-1 in South Africa, BR2 in Belgium, OSIRIS in France. A few additional research reactors meet local or regional requirements and can act as backups for world markets on a case by case basis. Most of the main production reactors are nearly half a century-old. Despite the refurbishment efforts made by their operators, they gradually reach the end of their operational lifetime.

Unscheduled stoppages of producing reactors are becoming more frequent and last for longer. As a result, supply problems for radionuclides have become more common and more acute since a few years. A **severe shortage** of production capacity of radionuclides is currently hitting the European nuclear medicine community, as well as globally.

The HFR reactor in the Netherlands is unavailable since August 2008 due to a technical failure of the primary cooling system of the reactor. The stoppage of this reactor is expected to last until mid-February 2009. The HFR reactor normally contributes to between 30 and 40% of the world medical radionuclide production. In addition, the IRE radionuclide processing facility in Belgium became unavailable in September 2008, nearly coincidentally with the HFR outage. The IRE is the second-largest world processor of radionuclides for medical use. No date has been announced so far for the restart of operations, which depends on the approval from the regulator. As a result of the unplanned outage of the HFR and of the IRE processing plant, shortages have arisen on the markets for medical radionuclides, which are expected to continue well into 2009. The actors on the radionuclide markets have taken short-term measures to limit the consequences as far as possible.

Meanwhile, the Canadian NRU and South African SAFARI-1 reactors have maximized their output, as did a number of other smaller scale producers, in order to alleviate the consequences of the supply deficit.

The short term supply crisis, which is not finished at the time of publication of this report, should be considered as a **serious warning signal**. This unprecedented supply crisis highlights the urgent need for a European strategy in order to compensate for the aging of most reactors used for medical purpose at industrial level.

Technical and licensing requirements will lead to the **decommissioning of most of the production reactors within the next ten years**. In the meantime, the demand for medical radionuclides will continue to grow. For instance, the world total of diagnostic procedures based on the most widely used radionuclide, ^{99}Mo, is today estimated to range between 25 and 30 million annually with a 1.5%-2.5% growth rate for the next ten years. The ^{99}Mo supply will remain critical for the next decade at least, since the techniques and equipment relying on 99mTc are used today in the vast majority of nuclear medicine procedures.

The access to the reactors and processing facilities for basic radionuclides has been a matter of concern for the nuclear medicine community for more than ten years, with numerous reports and expert reviews having alerted to the ever **growing risks of global supply disruption**. All such reports concluded that security of supply was progressively deteriorating. It has now become very urgent to establish agreements and structures at European level, as well as globally, to guarantee uninterrupted production of radionuclides for medical use.

In the short term, it is mainly a question of insuring the availability and the co-ordinated operation of the multipurpose nuclear reactors used for radionuclides' production, including under the auspices of AIPES.

For the long term, systemic solutions must be sought and implemented. The current generation of reactors with industrial output will be phased out within the next decade or slightly later, in the best case. Only one reactor is under construction today which shall be suitable for the purpose and which shall be operational in the timeframe under consideration, the RJH reactor in France.

Given the time span necessary for financing, siting, designing, licensing and erecting nuclear facilities in Europe, steps should be taken urgently to **identify and implement alternative solutions, not mutually exclusive**, such as:

- the partial or total conversion of existing research nuclear reactors into production reactors for radionuclides, such as e.g. the FRM-II reactor in Germany,
- the reliance of world markets on a network of "smaller" production reactors, with the resolution of associated logistic issues,
- the use of high-current accelerators & hybrid systems for the industrial production of radionuclides, SPECT, PET, therapy and pain palliation nuclides alike.

Some of those solutions might require a **change of paradigm**. The future expectations of the medical community and the mixed attitude of many public authorities towards the use of nuclear reactors, even for medical purposes, might result in a shift towards *non-reactor* radionuclides for both imaging and therapy purposes, and pain relief.

The events which have lead to the recent supply shortfall of major radionuclides could be far-reaching. They could entice the medical community and the industrial providers of technologies and services to gradually develop **new strategic orientations and priorities**, including e.g. an accelerated development of accelerator systems and networks for SPECT and PET nuclides. Such new orientations warrant detailed investigations, as they could necessitate profound adjustments of the current industry patterns. There is a worldwide potential for a gradual substitution of a system of decentralized production of radionuclides for the current centralized market pattern. All solutions will entail significant costs and will require adequate funding and public support.

The present study was launched by AIPES in mid-2008, following the announcement in May 2008 that development work of the MAPLE 1 & 2 reactors located at the Chalk River Laboratories in Ontario was stopped. Those reactors and the processing facility were intended to be dedicated to the production of medical radionuclides for world markets. The reactors and processing facility would have come on the radionuclide supply scene at the right time, as successors to aging facilities. The announcement of their abandonment changed totally the medium term outlook of supply assurance for radionuclides, triggering the present study.

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1. Short Term Risks and Long Term Challenges

1.1. The challenge: securing the needs for radionuclides (2010-2020)

Oncology, haematology, cardiology and neurology, among other disciplines, are areas using radionuclides for diagnostics, therapy and pain palliation routinely. Besides the established appliances of radionuclides in day-to-day medical practices, numerous radionuclides are widely used for radiopharmaceutical and fundamental R&D and for industrial applications.

Until the recent past, the continued supply of radionuclides for nuclear medicine was taken for granted by the majority of practitioners and by most representatives of the political class.

However, despite its importance in today's medical practices, the issue of medical radionuclide supply is at risk. As a matter of fact, radionuclides supply is crucially dependent on an unsustainably low number of large production reactors and processing facilities in Europe, in North America, in South-Africa and in Asia / Pacific. Most of those production plants are nearly half-century-old.

1.2. Current situation (October 2008)

A severe shortage currently hits the European nuclear medicine community, as well as globally, with the unavailability of the HFR reactor in the Netherlands due to a technical failure. The outage of this reactor is expected to last until at least mid-February 2009.

On 21 August 2008, the operator decided not to start up the HFR at the end of a month of major maintenance and inspections. A trace of gas bubble was detected in the primary cooling system during the course of these inspections, caused by corrosion of the pipe-work of the primary cooling system of the reactor.

The HFR reactor contributes to between 30 and 40% of the World medical radionuclide production. As a result of the unplanned outage of the HFR, shortages have arisen on the markets for medical radionuclides which will continue well into 2009. The actors on the radionuclide market have taken measures to limit the disturbances as far as possible. With the HRF out of service, continued supply will be limited.

In addition, the IRE radionuclide processing facility in Belgium, which is the second largest processor worldwide, became unavailable in September 2008, nearly coincidentally with the HFR outage. The IRE processing plant was shutdown as a result of a release of 131I gas, which was reported to the Belgian regulator Federal Agency for Nuclear Control on 25 August. The plant was shut down as a precaution. This occurrence has further intensified the current supply shortage, the more so since, technically, the material produced at the French reactor OSIRIS could only be processed at IRE's facilities, a bottleneck which has recently been removed. The IRE is the second-largest world processor of radionuclides for medical use. No date has been announced so far for the restart of operations, which depends on the approval from the regulator.

The current situation is exemplary of the short and long term risks faced by the nuclear medicine community with respect to supply of major radionuclides. At this moment in time, security of supply is not fully ensured, at the European level and worldwide.

- Among the approximately 250 research reactors operating in the world, only five (5) multipurpose reactors are able to produce radionuclides *on an industrial scale* for medical purposes, NRU in Canada, HFR in The Netherlands, SAFARI-1 in South Africa, BR2 in Belgium, OSIRIS in France.

- Beyond this list on industrial level, a few additional research reactors meet local or regional requirements and/or can act as backups and/or produce smaller quantities of radionuclides for world markets on a case by case basis, such as the FRM-II reactor in Germany, the OPAL reactor in Australia, the MURR reactor in the US, the HANARO reactor in Korea, the REZ reactor in the Czech Republic, the MARIA reactor in Poland, and some others.

- The technical and physical properties of the major radionuclides are such that the production reactors must have suitable operating conditions and adequate neutron flux. In addition, they must be located within reasonable distances of the processing facilities and hospitals which use them. Finally, the logistic chain must be robust at all times: transportation, regulation, chemical processing and drug manufacturing, etc. These criteria exclude from today's global picture most of the research reactors not listed above.

- The number of reactors producing radionuclides for nuclear medicine on an industrial scale is so small worldwide that risks for supply disruption exist during periods of the year when one or more of those reactors are shutdown for refuelling or maintenance or for any other operating reason.

- In such circumstances, any incident requiring stop of operation of the production reactors creates an immediate supply disruption, as the recent past amply demonstrates.

- The growing number of unscheduled outages of reactors in the recent months, with major repercussions for nuclear medicine activities worldwide, has demonstrated that severe supply shortage scenarios are more and more likely. Today, radionuclides supply for medical purposes is not 100% ensured at all times, be it in Europe, in North America or in Japan.

1.3 Long term: structural supply shortage ahead

Besides this short-term risk, supply of radionuclides for nuclear medicine will be *structurally* in jeopardy in the longer term, i.e. after 2015-2020.

- The major research nuclear reactors producing radionuclides on an industrial scale are getting close to the end of their operating lives. Many of them are more than 40 years old, after having been refurbished a number of times in order to cope with safety and regulatory requirements.
- Technical and licensing requirements will lead to the decommissioning of most of them within the next ten years.
- Operation of the Studsvik reactor in Sweden and the FRJ-II reactor in Germany, which were producing 5-10% of world demand, has already been stopped, respectively in July 2005 and May 2006.
- The OSIRIS reactor in France shall stop operation by 2015.
- The long-term fate of the veteran NRU reactor in Ontario and of the HFR reactor in the Netherlands is uncertain, not the least because of the recurrent incidents affecting their operation.
- There are uncertainties on the future of the BR2 reactor in Belgium, although the target decommissioning date is 2025, because the reactor might soon or later face the necessity to convert fuel from HEU to LEU, with associated costs and design adjustments.

The need for improvement of radionuclides supply is increasingly recognized in Europe. The current situation in Europe is paradoxical. The region was until very recently more than self-sufficient in respect of radionuclides production. Its industry was able to supply other world regions, being a net exporter. However, it now faces the challenge to secure reliable supply of some major radionuclides even in its own home market. One of the most acute issues is how to bridge the gap until next generation production facilities start operation, reactors or accelerators or hybrid systems.

Similar concerns are growing in the United States of America and in Japan about security of supply in the long term. The perceived risks have become more acute since May 2008, when the Canadian reactor projects Maple 1 and 2, which were to cover a significant part of the future requirements, have been abandoned by their developers. Replacement plans have not yet come to fruition in those parts of the world, like the facility planned by the University of Missouri-Columbia at its MURR reactor. Many American stakeholders urge the Federal Government to develop domestic sources of radionuclides for nuclear medicine[1]

[1] **Hugh Cannon, « Isotope Availability Task Group Releases Draft Report », The Journal of nuclear medicine, Vol. 49, N°8, August 2008, p.38N**

1.4. Industrial co-operation mechanisms

Until now, the industry has relied on informal co-operation mechanisms for optimizing the supply pattern and minimizing the risk of supply disruptions.

- One of these mechanisms is the AIPES-sponsored co-ordination of reactor operation schedules to ensure that at least one reactor is always running.
- Other mechanisms include informal contingency planning for alleviating the consequences of unforeseen supply shortages.
- There are also in place back-up supply agreements between major radiochemical producers and mutual alliances for back-up supply in order to alleviate the risk of interruption of supply to ^{99}Mo final users.

These mechanisms are working for the benefit of the nuclear medicine community and of the producers of radiopharmaceutical drugs, at low cost. However, those co-operation and backup devices are relatively fragile, since they involve market participants who are in intense competition with each other and who are permanently striving for market share. The two major supply crises of 2007 and 2008 have shown that the protection of commercial interests remains high on the agenda of market participants, even during crisis situations.

The market situation is idiosyncratic: in order to meet the risk adverse criteria of end-users, who request a 100% security of a supply 100% of the time, the reactor operators must maintain a significant over-capacity. Such over-capacity, which is a result of the redundancy needed to ensure continuity of supply worldwide, causes fierce competition between reactor operators and other market actors. It puts sustained pressure on prices. Hence, reactor operators and owners have few means to finance the development of the new facilities that will be needed to replace the aging reactors within the next decade. At this stage, one can speculate that a lack of adequate financing will result in a much lower degree of backup tomorrow.

It is an open question to what extent the end-users would be prepared to contribute today to the financing of those new facilities that will be needed for maintaining the security of supply they require, including their criteria for redundancy.

1.5. The AIPES survey

This report has been commissioned by the General Assembly of AIPES during its 2008 annual meeting in Brussels. The decision to commission this study was taken shortly after it was announced in May 2008 that the Canadian reactor projects Maple 1 and 2 had been stopped, an announcement which totally changed the medium term outlook of supply assurance for radionuclides.

The objective of the analysis requested by the AIPES governing board is to assess fission and activation of radionuclides requirements & supply for nuclear medicine for the period 2010-2020.

This assessment has been carried out between late June and early September 2008 by obtaining from each member of AIPES first-hand information on the future and possible issues in this respect. The information has been collected, analyzed, challenged and consolidated by an independent external consulting company, contractually bound by confidentiality.

The survey is based upon individual interviews with current and potential suppliers on their different options: reactor operators, radionuclides processors, radiopharmaceutical products suppliers, and other stakeholders, i.e. AIPES full members and AIPES associated members. As such, it aims at representing the collective wisdom of the members of AIPES who have been interviewed, with professional experience spreading over the entire spectrum of the medical radionuclide and imaging markets.

The present document is the report of **Phase 1** of the study, ending at the end of October 2008, which is devoted to an assessment of the supply & demand outlook 2010-2020 for the major radionuclide $^{99m}Tc/^{99}Mo$.

Phase 2 shall follow, with the aim of refining the analysis, including other radionuclides. Section 4 of the present document provides a proposed roadmap for Phase 2.

2. Radionuclides Demand for Medical Purposes

2.1. Common radionuclides for large scale use and production 2010-2020

A tentative list of main nuclides with large scale use during 2010-2020, and possibly later, is given in the table below. This table has been drafted on the basis of the opinions expressed by industry specialists interviewed in the course of this project, exercising their individual expert advice on the suitability for medical purposes, physical and chemical properties of elements, technical and logistical feasibility of large scale production and use. Only the *major* radionuclides, produced in both reactors and accelerators, are reported in the table.

- The most common radionuclides produced in reactors for which supply is believed to be in jeopardy for the period 2010-2020 are mentioned in **bold typeface**.
- The major concerns expressed during the interviews are about the supply outlook for the fission products ^{131}I and ^{99}Mo.
- In addition to these major reactor radionuclides, many other reactor nuclides for specific needs – including research and industry - have their supply jeopardized.
- The supply of radionuclides used for brachytherapy and external irradiation with sealed sources, although they were not part of this study, ^{192}Ir, ^{103}Pd, ^{60}Co, ^{90}Sr, ^{125}I, ^{252}Cf, and others, has been mentioned frequently during the present survey as a matter of concern for the near future.

Imaging: conventional, single photon emission tomography SPECT, SPECT/CT	Imaging: positron emission tomography (PET, PET/CT, PET/MRI)	Therapy, pain palliation, radioimmunotherapeutics	
^{67}Ga (a)	^{18}F (a)	^{67}Cu (a)	**^{131}I (r)**
^{99m}Tc/^{99}Mo (r)(g)	^{61}Cu (a)	**^{89}Sr (r)**	**^{153}Sm (r)**
^{111}In (a)	^{64}Cu (a)	^{89}Zr (a)	^{169}Er (r)
^{123}I (a)	^{68}Ga/^{68}Ge (a)(g)	**^{90}Y/^{90}Sr (r)(g)**	**^{177}Lu (r)**
^{131}I (r)	^{82m}Rb/^{82}Sr (a)(g)	**^{90}Y (r)**	**^{186}Re (r)**
^{133}Xe (r)	^{89}Zr (a)	^{117m}Sn (r)	**^{188}Re/^{188}W (r)(g)**
^{201}Tl (a)	^{124}I (a)	^{123}I (a)	alpha emitters, e.g. ^{213}Bi/ ^{225}Ac (g)(a)

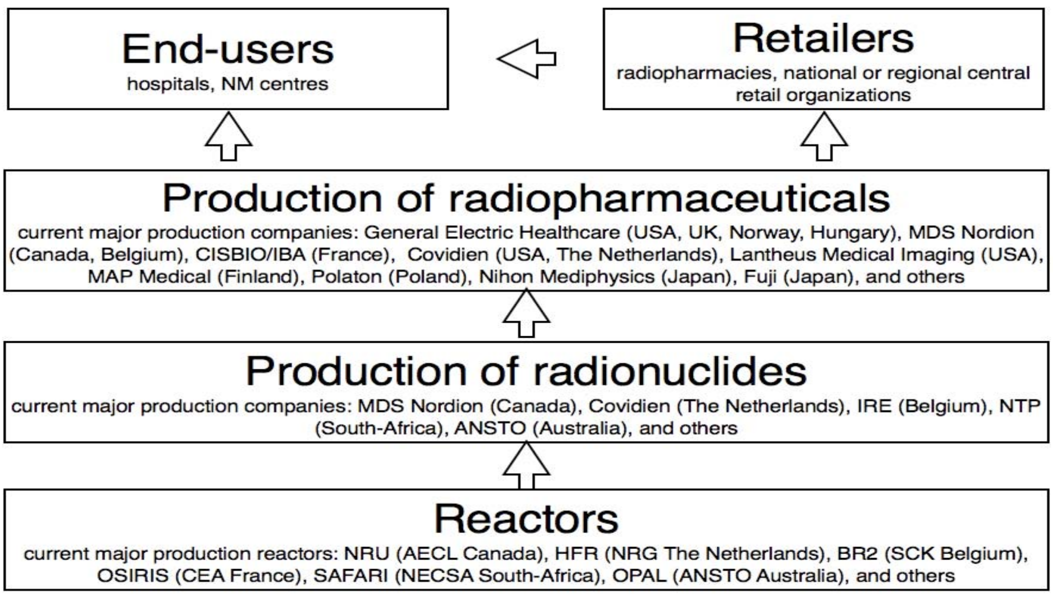
production route: **(r)** = reactor, **(g)** = generator, **(a)** = accelerator

2.2. Supply chain for ^{99m}Tc / ^{99}Mo

In this first phase of the AIPES study, the analysis concentrated on the supply and demand outlook for ^{99m}Tc /^{99}Mo only, for the following reasons:

- ^{99m}Tc is the most widely used radionuclide worldwide for nuclear medicine tomographic imaging techniques using single photon emission computed tomography (SPECT);
- in the view of all interviewees, ^{99m}Tc will remain a major radionuclide for nuclear medicine at least in the next 20 years;
- the market and supply chain of ^{99}Mo are mature; the economics are affordable for the health systems of most world regions, including in developing areas;
- no next generation of SPECT radionuclide is expected to breakthrough in the foreseeable future for possibly replacing the ^{99m}Tc / ^{99}Mo system;
- the recent achievements of hybrid SPECT/CT systems might provide a renewed impetus for imaging techniques using ^{99m}Tc;
- for the purpose of this study, ^{99}Mo is a good example of the issues relevant to nearly all others radionuclides produced by nuclear fission and activation in a neutron reactor flux;
- if ^{99}Mo supply is secured, supply for most other radionuclides of interest (from reactors) in the medium term may also be secured.

The supply chain for ^{99}Mo, with mention of the main actors on world markets is sketched on the diagram hereunder.



Worldwide, the market is characterized by:

- a small number of market actors;
- a very high scientific and technical level for all activities, from production in a nuclear reactor to medical utilization by end-users;
- very heavy investments at all stages;
- a dependence on production reactors that are devoted to many unrelated activities, such as basic nuclear science, irradiation for industrial uses, materials science, nuclear waste management research and innovation;
- a strong interdependence of market actors among themselves and with governmental bodies;
- a strong interaction with international policy making, notably nuclear non-proliferation policies;
- a market environment combining the specificities of healthcare industries and of nuclear industries, with respect to licensing, approvals;
- the need for efficient logistic chain, efficient location of production and processing facilities, necessity to ensure short processing and transportation times, with a very high level of quality assurance.

2.3. Conventional nuclear medicine procedures using ^{99m}Tc / ^{99}Mo (1990-2020)

The following paragraphs of this section give estimates of worldwide demand for ^{99}Mo, based on interviews with the major market actors. The global picture necessarily clouds some of the specific features of the major regional markets. For the purpose of this report, one distinguishes between four major regional markets[2].

Those are:

- Europe, comprising the European Union with Switzerland, Norway, Iceland, the Balkan countries and Turkey;
- North America, comprising the three NAFTA countries;
- Asia / Pacific, comprising Japan, South Korea, Taiwan, Australia;
- Others: India, Pakistan, Middle East, Africa, South America and all world regions not mentioned above.

The graph on Fig. 1 below provides estimates of the past and future use of conventional nuclear medicine procedures with $^{99m}Tc/^{99}Mo$ for the period 1990-2020. These are estimates based upon expert opinion of interviewees and not the result of detailed surveys. Where possible they are based on AIPES member's own individual projections, otherwise collective AIPES assessments are used. Although those estimates must be used with some caution, they are believed to be reasonably representative of the development of nuclear medicine procedures using ^{99m}Tc/ ^{99}Mo during the near past and for the medium term.

[2] ***The report does not cover the Russian Federation, China and the central Asian countries, for which meaningful data are not available or not sufficiently reliable.***

Since the supply chain for $^{99m}Tc/^{99}Mo$ and the use of ^{99m}Tc in daily nuclear medicine procedures worldwide are well established, the prospect exists for further utilization of $^{99m}Tc/^{99}Mo$ within the forecast period of this report (2010-2020) and beyond.

Currently (2008), the world total of *in vivo* diagnostic procedures using ^{99m}Tc is estimated to range between 25 and 30 million annually. Europe represents approximately 6-7 million procedures, North America 12-15 million, Asia / Pacific 6-8 million, and other world regions 0.5 million . The strong growth experienced since the early 1970s is not expected to continue from 2010 onward. The forecast, with annual growth rate of 1%-2%, suggests that a period of fast development is now followed by consolidation. This growth rate could become higher in case of fast growth of SPECT/CT systems or lower if a substitution in favour of e.g. PET radionuclides or other imaging technologies takes place on a large scale.

For the other reactor radionuclides used in therapy, pain palliation, diagnostics and research, demand is forecast to continue to increase, at varying rates depending on the specific nuclide. These segments of the demand have not been examined in detail in Phase 1 of the present study. Requirements for reactor radionuclides such as 153Sm (used for pain palliation, bone cancer therapy), 90Y, 169Er and possibly 186Re (arthritis and synovitis therapy), and others, continue to grow, following the general trend towards widespread utilization of nuclear processes for therapy.

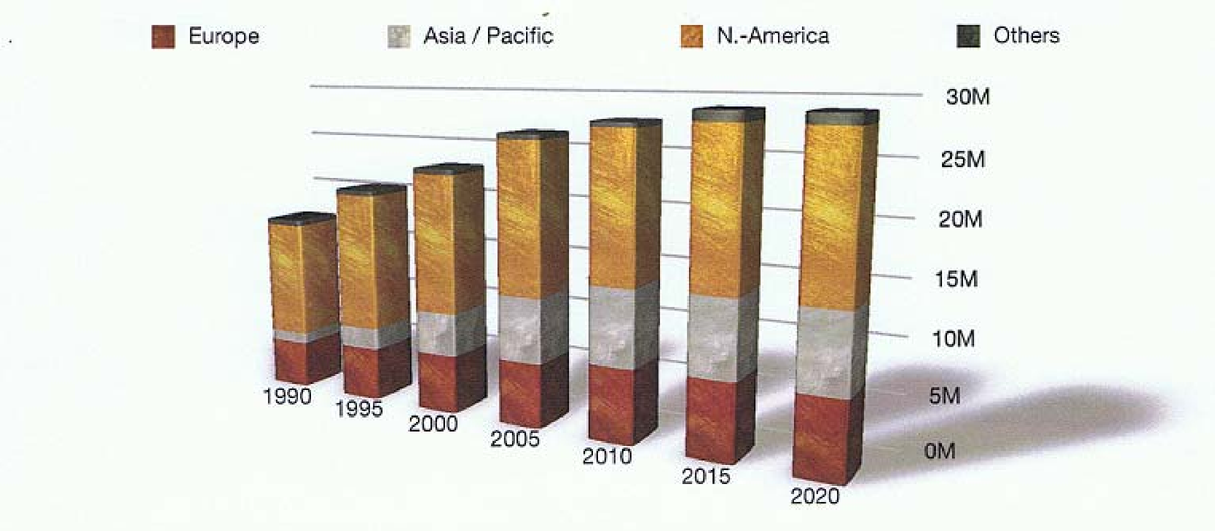


Fig 1. - Estimated in vivo *nuclear medicine procedures with $^{99m}Tc/^{99}Mo$, lab tests excluded, for major world regions 1990-2020 (million procedures per year).*

2.4. Growth of ^{99}Mo requirements (1990-2020)

The relationship between the number of nuclear medicine procedures using ^{99m}Tc and the quantities of ^{99}Mo required is neither straightforward nor proportional. The graph in Fig. 2 below shows estimates of the quantities of ^{99}Mo delivered to end users and forecast until 2020. The quantities are expressed in TBq per week, normalized at *t+6* days, where *t* is the time of despatch from the ^{99}Mo producer[3]. For reference, Fig. 3 shows the same data expressed in Ci per week. Currently, on the average, the world total requirement of ^{99}Mo is estimated to range between 370 TBq and 450 TBq weekly [10,000 and 12,000 Ci], normalized at *t*+6d. The pie chart in Fig. 4 shows that Europe represents approximately 22% of this total, North America 52%, Asia / Pacific 20%, and other world regions 6%.

Even with the AIPES modestly optimistic assumptions about the growth of ^{99m}Tc/^{99}Mo use, there will be a continued need to ensure secure supply during the forecast period of this report and beyond. The final users of radionuclides for nuclear medicine expect the supply chain to be able to meet the demand now and in the long run.

The number of supply chain participants is limited on both the demand and the supply sides, with the establishment of a bilateral oligopoly (few sellers-few buyers) with fierce competition among sellers. The purchasing behaviour of the producers of radioactive pharmaceuticals, who are themselves sellers of technetium generators to final users, is in this respect a determining factor. For a variety of reasons, it is unlikely that the number of suppliers at industrial level will drastically increase in the short term. The number of reactors suitable for radionuclide production has declined sharply in Europe since 10 or 15 years; the number of individual processing facilities follows the same trend.

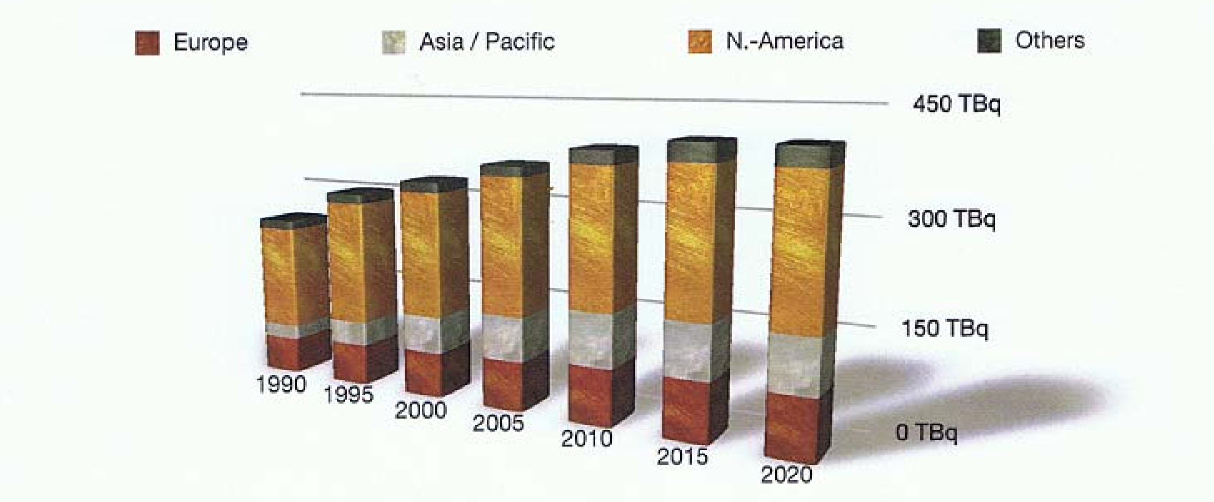


Fig 2. - Estimated average weekly quantities of ^{99}Mo delivered to end-users for major world regions 1990-2020 (TBq per week average, normalized at t+6 days).

[3] ***Depending on the respective locations of the production reactors and of the chemical processing faciliites, the time span between (a) end of irradiation / end of bombardment (EOvEOB) and (b) the time t mentioned in the tewxt may range from 22 to 48 hours or een more in some instances. The data shown on the graph may thus not be used without precautions in order to estimate the activities at the time of unloading of targets from the reactors.***

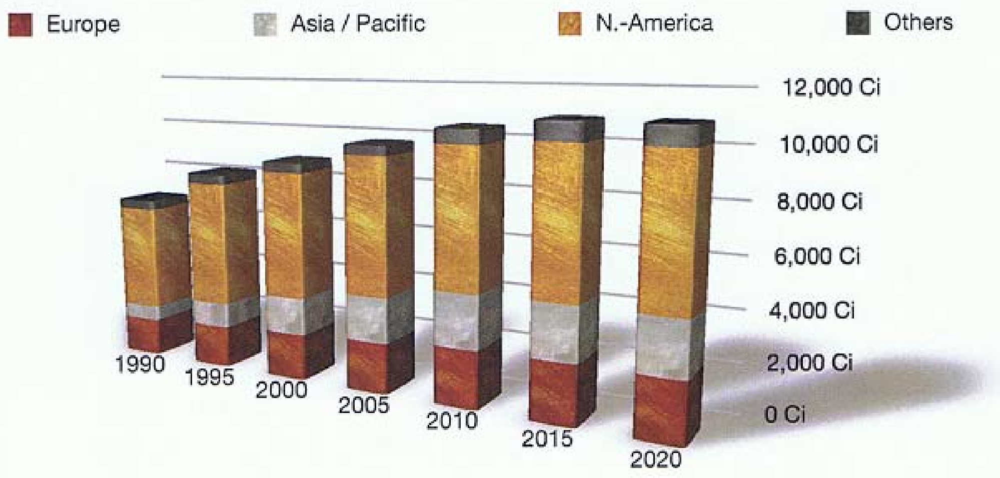


Fig 3. - Estimated average weekly quantities of ^{99}Mo delivered to end-users for major world regions 1990-2020 (Ci per week average, normalized at t+6 days).

2.5. Degree of redundancy

The medical community and their patients expect that the supply of radiopharmaceutical products for diagnostic & therapeutic & pain palliation purposes be ensured totally, without interruption, 100% of the time.

The demand side of the market is completely risk adverse. In order to secure supply in accordance with such stringent criteria, the market has in principle several means.

Constitution of inventories: There is no possibility to keep inventories of radionuclides for nuclear medicine, because of their radioactive decay. The constitution of buffer stores between reactor production and utilization of radionuclides for nuclear medicine is technically impossible.

Diversification of suppliers: The potential for diversification of suppliers will probably not be very different in the near future from what it is today, except if a significant change of paradigm occurs in the next few years. It is unlikely that many new entrants will produce radionuclides for nuclear medicine in significant quantities in the coming years and will be transporting the products to consuming areas, safely and regularly.

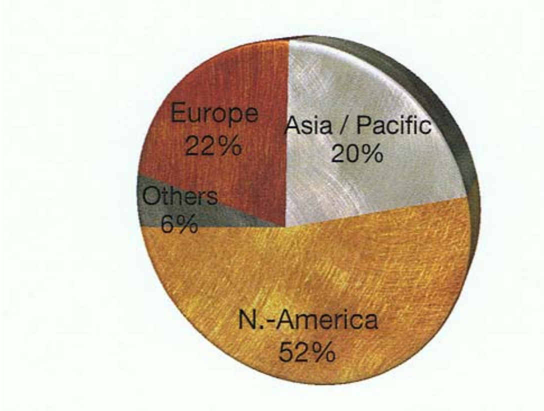


Fig 4.- Estimated shares of quantities of ^{99}Mo delivered to end-users in major world regions 2007[4].

The number of potential suppliers at industrial scale will probably remain limited, as will be the number of reactors capable of meeting the demand and the number of suitable processing facilities. The situation could change if more reliance is put on "smaller" reactors or on a network of high-current accelerators capable of producing a range of radionuclides in the quantities required.

In the US, where there are currently no reactors that are dedicated to irradiation of targets or 99Mo production and no processing facilities for 99Mo recovery, there are numerous pleas in favor of new radionuclides production facilities. The concerns expressed by the US medical community could lead to the use of the MURR reactor[5] and to the search of other options in the US. This would increase the diversification potential offered worldwide to the producers of radiopharmaceutical drugs.

Redundancy of capacity production: A certain degree of redundancy of production capacity in reactors is the only practical way to guarantee today that the reactor operators will be able to meet the requirements of the nuclear medicine community with respect to security of supply of radionuclides.

The exact degree of redundancy is a matter of collective judgement of the market actors. It depends on objective factors and on consideration of past experience, such as the number of reactors and processing plants for production radionuclides on an industrial scale, their respective market shares, the track record of each of them regarding continuity of supply, the likelihood that any of those would disappear from the marketplace for whatever reason, including discontinuation of reactor operation, temporarily of permanently.

In the current status of the market, with very few commercial production reactors and few processing facilities, an opinion held by most market actors is that a redundancy of approximately 250% is appropriate. In other words, the peak production capacity of radionuclides at reactors and processing facilities should be at least equal to 2.5 times

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[4] Background data for this chart are expressed in Ci per week average, normalized at t+6 days

[5] The MURR reactor is a multipurpose test facility in operatin since 1966 in Missouri. It is currently used, among others, for the production of other radionuclides than 99Mo. Under some conditions, such as the building of a processing facility in its vicinity, the MURR reactor could provide 40% or 50% of the US domestic 99Mo market.

requirements worldwide. On a regional level, the preferred redundancy level might be even higher, given the reliance on fewer producers within reasonable geographical distances.

The level of security of supply not only depends on the theoretical redundancy rate but also on the absolute number of suitable reactors & processing facilities and on the details of their operational schedule. For instance, the list of important parameters includes the cycle lengths, the number of cycles per year, the duration of the normal shutdown time, the duration of any special shutdown time, the weekdays of cycle start and end, and others.

Redundancy has a cost. The security of supply brought by full size backup solutions with a 250% redundancy must be paid for. Multipurpose research reactors, either existing, under construction or planned, could in principle be able to accommodate target irradiation for nuclear medicine with or without design changes but always with additional costs.

3. Radionuclides Supply Capacities

3.1. Reactor production of ^{99}Mo (2007 data)

Estimates have been made of the number of targets irradiated in 2007 at the main reactors for production of ^{99}Mo. The regional share is shown on Fig. 5.

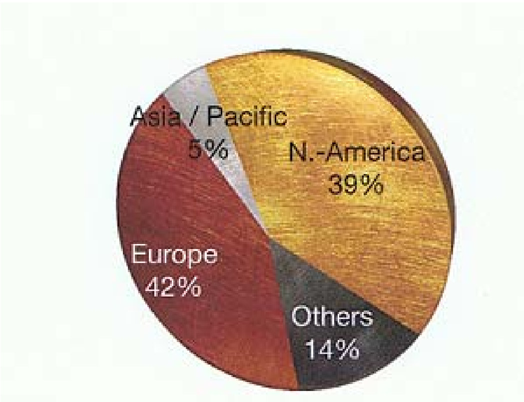

Fig. 5. - Estimated 2007 regional shares of current reactor production of ^{99}Mo

Taking into account the physical features of the reactors and some assumptions about the world market for ^{99}Mo, the quantities of material produced worldwide has been estimated for 2007. Fig. 6 illustrates the regional breakdown of the ^{99}Mo production at reactors in 2007, calibrated at *t*+6d, where *t* is the time of despatch from the processors, processing losses deducted. These data are directly comparable with the worldwide demand figures estimated earlier in this report. This graph shows the structural regional imbalance between consumption and production.

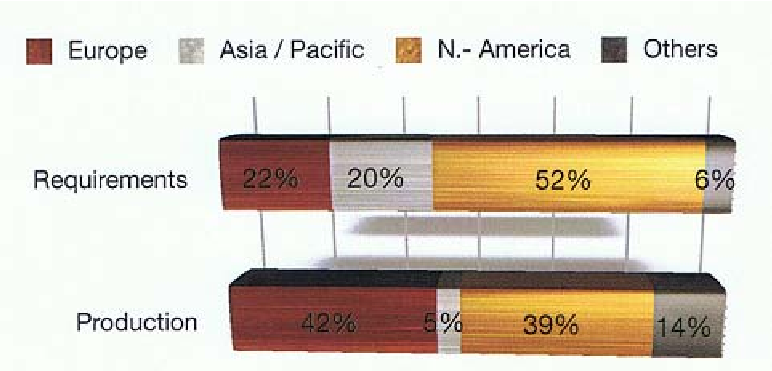

Fig. 6. – Estimated 2007 regional shares of current reactor production & requirements of ^{99}Mo[6]

3.2. Reactor production of ^{99}Mo (October 2008 data)

Figures 7 and 8 show how regional shares of production have been modified as a result of the current supply crisis. These charts provide estimates for a situation which is highly volatile, changing from week to week. They provide only a rough image of the very recent market evolutions. It is clear that the production patterns are being modified significantly, with the major world regions production shares getting closer to self-sufficiency criteria. In addition, “smaller” producers are also playing a significant role for alleviating the consequences of the supply problems. The Canadian NRU and South African SAFARI-1 reactors have maximized their output, as did a number of other smaller scale producers, in order to alleviate the consequences of the supply deficit.

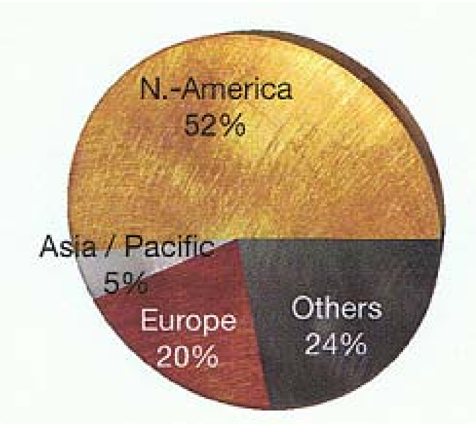

Fig. 7. - Current regional shares of current reactor production of ^{99}Mo, data estimated for October 2008, adjusted for current supply crisis

[6] *Background data for this graph are average weekly values expressed in Ci/week, calibrated at t+6d.*

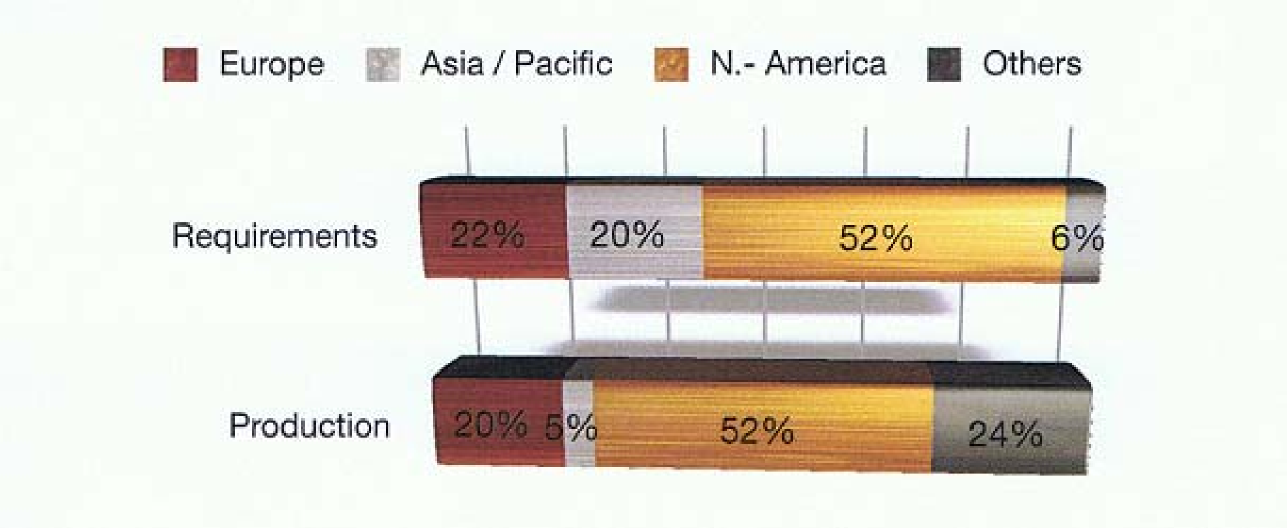

Fig. 8. - Current regional shares of current reactor production & requirements of ^{99}Mo, data estimated for October 2008, adjusted for current supply crisis

3.3. Supply capacity 2010-2020

The AIPES does not attempt to forecast actual annual production of ^{99}Mo or other radionuclides for nuclear medicine, but focuses instead on production capacity which is carefully defined. Specifically, for each reactor and each processing facility, one estimates the maximum annual and weekly output attainable based on technical, licensing and policy factors known at the time the forecast is developed. The technical factors include the neutron flux, main characteristics of the reactor core, the design thermal power capacity, the yearly load factor, i.e. the duration available for irradiation, the geographical location with respect to the processing facilities, the number of positions and channels available for nuclear medicine, recovery losses at treatment facilities, and others. The forecast is based on information provided by reactor operators & radionuclides producers or, as the case may be, by published sources.

A recent inventory of pertinent reactors, with their characteristics, is given in a NEA report[7] of 2004. The following section reports only on some important existing or potential industrial sources of radionuclides for nuclear medicine, focussing on ^{99}Mo supply, as consistently in the present Phase 1 of the AIPES study[8]. The three summary tables below provide some main features of those reactors.

[7] AEN/NEA, Beneficial Uses and Productin of Isotopes, 2004 Update, Published 25-FEB-05, 64 pages, NEA#05293, ISBN : 92-64-00880-2.

[8] See also the list compiled by Lawrence Kidd, « Curies for patiens », Nuclear Engineering International, July 2008, p. 26-32

Major current radionuclide production reactors Country / location	Name	Design thermal power MW	Max Thermal flux n $cm^{-2}s^{-1}$	Fuel	Criticality month	Status	Operating days per year (nominal)
Belgium, Mol	BR2	100	$1x10^{15}$	93% HEU	Jun-61	Oper. (age 47)	120
Canada, Chalk River	NRU	135	$4x10^{14}$	20% LEU	Nov-57	Oper. (age 51)	270
France, Saclay	OSIRIS	70	$2x10^{14}$	20% LEU	Sep-66	Oper. (age 42)	180
Netherlands, Petten	HFR	45	$2x10^{14}$	20% LEU	Nov-61	Oper. (age 47)	270
South Africa, Pelindaba	SAFARI-1	20	$2.4x10^{14}$	20% LEU (conversion underway)	Mar-65	Oper. (age 43)	310

Other current radionuclide production reactors Country / location	Name	Thermal power MW	Thermal flux n $cm^{-2}s^{-1}$	Fuel	Criticality month	Status	Operating days per year (nominal)
Australia, Lucas Heights	OPAL	20	$3.0x10^{14}$	20% LEU	Aug-06	Oper. (age 2)	?
Czech Rep., Rež	LVR-15	10	$1.5x10^{14}$	36% HEU	Sep-57	Oper. (age 51)	200
Germany, Munich	FRM-II	20	$8x10^{14}$	93% HEU	Mar-04	Oper. (age 4)	250
Korea, Taejon	HANARO	30	$4.5x10^{14}$	?	Feb-95	Oper. (age 13)	150 ?
Poland, Otwock-Swierk	MARIA	30	$4.5x10^{14}$	36-80% HEU	Dec-74	Oper. (age 34)	280
Argentina, Ezeiza	RA-3	5 -10	$1x10^{14}$	20% LEU	Aug-68	Oper. (age 40)	230
USA, Columbia, Missouri	MURR	10	$6x10^{14}$	?	Oct-66	Oper. (age 42), currently, no ^{99}Mo production	280 ?

Major potential future radionuclide production reactors Country / location	Name	Thermal power MW	Thermal flux n $cm^{-2}s^{-1}$	Fuel	Criticality month	Status	Operating days per year (nominal)
France, Cadarache	RJH	100	$6x10^{14}$	20% LEU	-	Under constr. (oper. 2015)	250 ?
Reactors under consideration / planned : PALLAS (Netherlands), MYRRHA (Belgium), SAFARI-2 (South-Africa), ...							

3.4. Supply security outlook

The access to the reactors and processing facilities for basic radionuclides has been a matter of concern for the nuclear medicine community for more than ten years, with numerous reports and expert reviews having alerted to the ever growing risks of global supply disruption[9]. All such reports concluded that security of supply was progressively deteriorating, for the same reasons as those reported in the present document. It has now become very urgent to establish agreements and structures at European level, as well as globally, to guarantee uninterrupted production of radionuclides for medical use.

In the short term, it is mainly a question of insuring the availability and the co-ordinated operation of the multipurpose nuclear reactors used for radionuclides' production. It is expected that enhanced dialogue between national & European authorities, and producers of radio-pharmaceuticals, will result in better coordination from now onwards. The industry participants might agree on a set of compliance principles for responsible behaviour in order to avoid severe short term consequences of shortage conditions.

The graph in Fig. 9 shows the distribution of world research reactors commissioned from 1955 to 2000, according to the IAEA research reactor database. The major reactors used for current production of radionuclides for nuclear medicine have been commissioned during the first & second decades on this graph. Technical and licensing requirements will lead to the decommissioning of most of them within the next ten years.

It is a misconception to believe that the existing large production reactors will continue operation much beyond their 'normal' lifetime. It is certain that OSIRIS in France, for example, shall be shutdown by 2015. The regulatory authorities in Europe are not expected to grant license extensions for aging facilities without requiring compliance with current state-of-the-art safety standards, a position endorsed by the industry. In the near future, new production reactors and new processing facilities will be needed in replacement, beyond any doubt. The only reactor under construction today which shall be suitable for the purpose and which shall be operational in the timeframe under consideration, is the RJH reactor in France. The RJH reactor, once in operation, could provide approximately 25% of the current European radionuclide production on a routine basis and up to 50% in particular circumstances.

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[9] A few examples are the following : Frost & Sullivan, FFTF Medical Isotopes Market Study 2001-2020, 20 November 1997 (jnm.snmjournals.org/cgi/reprint/39/2/27N ;pdf) ; AEN/NEA, Beneficial Uses and Production of Isotopes, 2004 Update, 25-Feb 2005, 64 pages, NEA#05293, ISBN: 92-64-00880-2, USDOE Expert Panel: Forecast Future Demand for Medical Isotopes, March 1999, (www.ne.doe.gov/nerac/neracPDFs/isotopedemand.pdf); Arthur Andersen & Co. Worldwide Isotope Market Update, November 1994 (quoted in the 1999 DOE report); SNM, National Radionuclide Production Enhancement (NRPE) Program: Meeting Our Nation's Need for Radionuclides, January 2005; European Commission DG JRC, Radioisotope Survey, EUR 21874 EN, October 2005 (ie.jrc.ec.europa.eu/downloads/file.php?id=32).

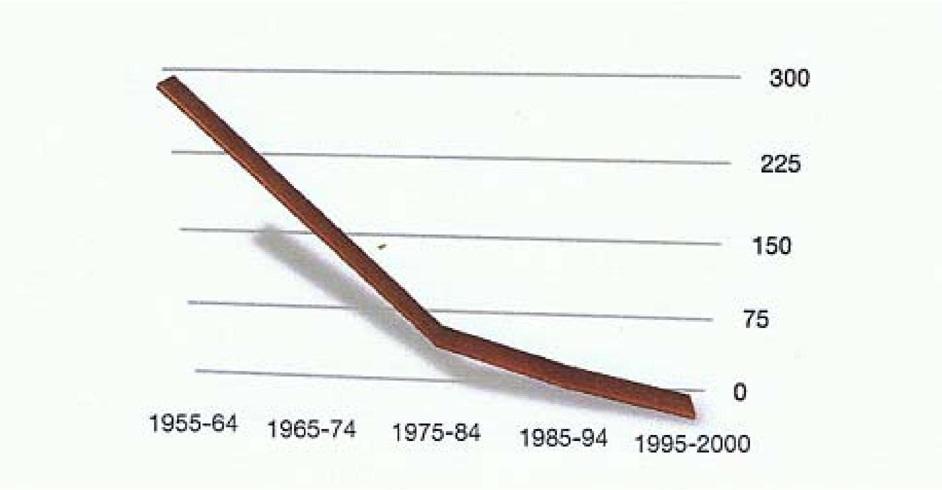

Fig. 9. - Research reactors commissioned per decade (all reactor types - source: IAEA)

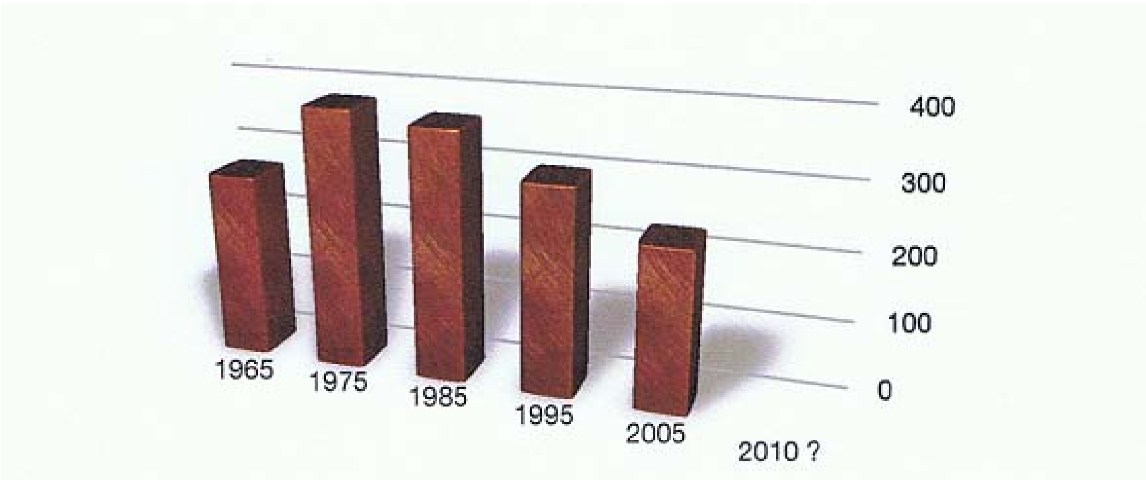

Fig. 10. - Number of operating research reactors worldwide (all reactor types)

3.5. Search for solutions - or a change of paradigm?

Given the time span necessary for financing, siting, designing, licensing and erecting nuclear facilities in Europe, steps should be taken urgently to decide and to build the new multipurpose or dedicated facilities that are critically needed. Alternative solutions should be explored, such as the partial or total conversion of existing research reactors into production reactors for radionuclides (such as the FRM-II reactor in Germany), the reliance of world markets on a network of “smaller” production reactors, with the resolution of the associated logistic issues, and the use of accelerators and hybrid systems.

The time is now very close for decision making. Short term and long term risks are growing that nuclear medicine community will experience more severe and more frequent shortages of radionuclides supply. The crucial years in that respect are between today and 2020. Both in Europe and worldwide, major risks with respect to continuity of supply of radionuclides for medical purposes will be faced in that timeframe if no new radionuclide production means are made available.

A number of solutions exist in theory, such as:

- to extend the operating life of existing multipurpose reactors in compliance with modern safety requirements,
- to build and operate new reactors (partially) dedicated to radionuclides production,
- to convert younger existing research reactors into radionuclide production reactors, partially or totally,
- to identify, assess and possibly design and implement alternative processes for production of radionuclides, if any, in the quantities needed and with the same quality level, including accelerators and hybrid facilities,
- to gradually use alternative radionuclides and alternative imaging technologies, such as e.g. ultrasonic echography, positron emission tomography, imaging techniques based on magnetic resonance, and others.

3.6. Economics of reactor systems

All solutions will entail significant costs and will require adequate funding. The economic merits and financial requirements of the main solutions and their various combinations have not been assessed in this study. Suffice it to report here that radionuclides production for medical purposes at *reactors* is mostly a by-product of other activities, such as nuclear research, material science or training. This is also the case for the FRM-II reactor in operation in Germany and for the forthcoming French research reactor RJH currently under construction[10]. And likewise for any multipurpose reactor project contemplated for the future, such as PALLAS in The Netherlands[11], MYRRHA in Belgium, etc.

In those cases, the quantities of radionuclides needed for the medical uses, and thus the financial weight of their production, must be balanced with the other interests at stake. In other words, the decision to build and operate new reactors generally depends only partially on the radiopharmaceutical customers. However, if appropriate funding is provided for medical radionuclide production, this may become a winning argument for keeping current reactors operating or for converting younger reactors to radionuclide production.

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[10] Construction cost estimated by the operator CEA for RJH in May/June 2005 : approx. 500 million euros ; estimate unchanged since then, see e.g. http///www.world-nuclear-news.org/NN-European_materials_Test_reactor_progress-0107088.html dated July 2008.

[11] Construction cost estimated by the operator NRG for PALLAS in October 2008 : approx. 300 million euros.

3.7. Substitution

The achievements of hybrid SPECT/CT systems, together with the existing broad spectrum of SPECT radiotracers, might provide a second life for imaging techniques using nuclides produced in reactors[12]. The techniques and equipment relying on ^{99m}Tc are used today in the vast majority of nuclear medicine procedures. In principle, they will still be needed in the long term.

There is however potential for substitution. The future expectations of the medical community and the mixed attitude of many public authorities towards the use of nuclear reactors, even for medical purposes, might result in a shift towards *non-reactor* radionuclides for both imaging and therapy purposes, and pain relief. The events which have lead to the recent supply shortfall of major radionuclides could be far-reaching. They could entice the medical community and the industrial providers of technologies and services to gradually develop new strategic orientations and priorities. Such new orientations warrant detailed investigations, as they could necessitate profound adjustments of the current industry patterns. The relative merits of those approaches will be assessed during Phase 2 of the present AIPES study (see Section 4 hereinafter).
Alternative methods for imaging and therapy show an exponential growth, e.g. positron emission tomography (PET, PET/CT), magnetic resonance imaging, ultrasonic echography and others. Until very recently, in the common view of practitioners and industrialists, these methods added only new layers of diagnostic, therapeutic or pain palliation technologies but were not to *replace* 'conventional' nuclear medicine procedures, i.e. using radionuclides produced by fission of uranium or by activation of materials in a nuclear reactor core.. The recent supply crises of ^{99}Mo (December 2007 and August-October 2008) could contribute to a change in perspectives. As a result of the mixed outlook for new reactor projects for the period under consideration, the alternative methods mentioned above are increasingly being considered by the medical community as *substitutes* for the conventional nuclear medicine procedures instead of as complementary methods, as previously.

✓Steps should be taken urgently, to decide, to build, to license and to operate *new facilities and networks in Europe* that could produce radionuclides for nuclear medicine, in order to replace the aging production reactors.

✓All alternative solutions should be explored, such as the dedication of existing research reactors to production of radionuclides, the partial or total conversion of existing research nuclear reactors into production reactors for radionuclides, the reliance of world markets on a network of "smaller" production reactors, with the resolution of associated logistic issues, the use of high-current accelerators & hybrid systems for the industrial production of radionuclides.

✓*Public-private partnerships* (PPP) and *international consortiums* should be considered for securing the financing of the new production facilities and networks which are needed for Europe to remain self-sufficient in radionuclides for nuclear medicine.

[12] See the review paper of Andreas K. Buck et al., « SPECT/CT », The Journal of Nuclear Medicine, Vol.49, N° 8, August 2008, p.1305-1319.

✓The issue of interrelations between multipurpose reactor use for *research* and for *radionuclide production* should be dealt with and solved to the best interest of all parties.

✓The issue of r*edundancy of supply capability* should be addressed collectively and solved to the best interest of all market participants and stakeholders, including the patient, the medical community and the taxpayer.

4. Proposed Terms of Reference for Phase 2

The AIPES intends to explore a number of routes in order to alleviate the risks associated with supply shortages of radionuclides for nuclear medicine, both short term and long term. The ultimate goal is to identify for Europe (and possibly globally) a much more secure supply system of radionuclides for nuclear medicine than nowadays.

The proposed objectives for Phase 2 of the AIPES study are:

- To identify and assess long-term *robust solutions* to Europe's future radionuclide production forecast structural shortage. The emphasis will be on ensuring self-sufficiency for Europe within the global picture.
- To build a *consensus view* on the range of solutions that AIPES would promote in front of public authorities and other stakeholders.
- To define, with the detail and precision needed, the *position that AIPES will take* in the debates that shall be held with public authorities and other stakeholders on the policy to be developed for the future of the radiopharmaceutical industry in Europe.
- To perform a risk assessment for future supply from the main existing and prospective radionuclide production facilities and networks in Europe and elsewhere, their timeframe and their economic and social feasibility.
- To examine other constraints on supply, such as transportation and logistics, product adequacy and quality, geopolitical constraints, environmental, non proliferation and social risks.

“Report on Molybdenum-99 Production for Nuclear Medicine – 2010 – 2020”
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