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Medical Applications of a Nuclear Reactor

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Abstract: Nuclear reactors are usually associated with the production of energy, but some reactors, including the reactor facility of the University of Technology Delft, The Netherlands, are being used for scientific research. This review describes the current possible applications of such a research facility in medicine. This concerns in the first place the production of various nuclides and chemical carriers, which are now widely used in clinical medicine. Both α and β emitters can be effective in the treatment of tumors and metastases, while γ-emission allows imaging of organs and activity of biological processes. A less well-known application of a research reactor is instrumental neutron activation analysis (INAA), a technique for qualitative and quantitative multi-element analysis of major, rare and trace elements in all kinds of materials, including those from human origin such as blood, nails, hair and tissue samples. In contrast to mass spectrometry, INAA is not restricted to measurement in small samples, since even large samples up to kilograms can be analyzed. This is especially of importance when an element is not distributed homogeneously in materials. INAA is also used in biomonitoring to measure the burden of toxic chemical compounds and elements in biological substances. A promising development is the use of enriched stable isotopes, an attractive alternative for the application of radioactive tracers in the study of the bioavailability and distribution of essential trace elements and metals in the human body.

Keywords: Nuclear Research Reactor, Instrumental Neutron Activation Analysis, Enriched Stable Isotopes, Radionuclides

1. Introduction

Nuclear reactor facilities are usually associated with energy production and not with healthcare. And if this association between reactors and healthcare is made, it is often a negative one based on a general fear of ionizing radiation and on historic accidents as in Tsjernobyl and Fukushima. However, some nuclear reactors, such as the 2.3 MW reactor of the TU Delft (Reactor Institute Delft (RID)), are designed for research and contribute to a variety of sciences including those in the field of healthcare and environment. The main application concerns the production of radioactive isotopes, which are now widely used both in research and clinical medicine. Another application, instrumental neutron activation analysis, allows multi-element analysis in all kind of materials including those from human origin. With the introduction of enriched stable isotopes a new method has become available to trace elements in the human body without exposure to ionizing radiation. Such enriched stable isotopes can be measured with instrumental neutron activation analysis (INAA) making use of a reactor facility. This review focuses on these new developments with promising implications for medical research.

2. Review

2.1. Isotopes and Radionuclides

At this moment 118 chemical elements have been identified, of which the first 94 occur naturally on Earth with the remaining 24 being synthetic elements [1]. The smallest particle of an element is an atom with the number of protons in its nucleus defining the property of the element, referred to as atomic number. All isotopes of a given element have the same number of protons but differ in the number of neutrons. The neutron number has large effects on nuclear properties, but its effect on chemical properties is usually negligible [2]. Most elements have at least one stable isotope, while 38 have exclusively radionuclides, which decay over time into other elements. In case more than one stable isotope of an element exist, their naturally occurrence, and therefore their mutual ratio, is more or less stable, although small variations may occur. As an example, the element iron (Fe) has four stable isotopes: ^{54}Fe (26 protons and 28 neutrons), ^{56}Fe (26 protons and 30 neutrons), ^{57}Fe (26 protons, 31 neutrons) and ^{58}Fe (26 protons and 32 neutrons) with a naturally occurrence of respectively 5.4%, 91.7%, 2.2% and 0.3% [3]. In contrast to stable isotopes, radionuclides or radioactive isotopes have an excess of nuclear energy making them unstable. This excess energy can be used in one of three ways: 1) emitted from the nucleus as gamma radiation, 2) transferred to one of its electrons to release it as a conversion electron or 3) used to create and emit a new particle (alpha or beta particle) from the nucleus [4]. These emissions are considered ionizing radiation because they are powerful enough to liberate an electron from another atom. Radionuclides occur naturally or are artificially produced in nuclear reactors, cyclotrons, particle accelerators or radionuclide generators. In a reactor, radionuclides are produced as an unavoidable result of nuclear fission or are deliberately produced, exploiting the high flux of neutrons present, to activate elements placed in the reactor. Radionuclide generators contain a parent radionuclide that decays to produce a radioactive daughter. The parent is usually produced in a nuclear reactor. A typical example is the technetium-99m generator used in nuclear medicine with the parent molybdenum-99 produced in the reactor.

In today's medical practice, the application of radionuclides can hardly be overestimated. Radioactive chemical tracers emitting gamma rays or positrons provide diagnostic information about internal anatomy and the functioning of specific organs. They are used in techniques such as scintigraphy, single-photon emission computer tomography (SPECT) and positron emission tomography (PET). More than 100 radionuclides have now been used in medicine, most commonly administered intravenously such as technetium-99m, iodine-123 and -131, thallium-201, gallium-67 and fluorine-18, while xenon-133 and krypton-81m are used as gaseous radionuclides [5]. Apart from imaging, radionuclides are more and more applied in the treatment of tumors and metastases making use of the effects of alpha and beta radiation. This group includes e.g. iodine-131 (thyroid related disorders), radium-223 and rhenium-186 and -188 (bone metastases), yttrium-90 (lymphomas, pancreatic cancer), holmium-166 (tumors in the liver) and phosphorus-32 (ovarian cancer). In radioimmunotherapy monoclonal antibodies directed against tumor-associated antigens, such as prostate-specific-membrane antigen (PSMA) are used to bring the radionuclide to its target to increase the effectiveness of therapy and to limit "collateral damage".

Radioactive isotopes such as chrome-51, indium-111 and iron-59 have also been used as tracers to study survival time of erythrocytes and thrombocytes and iron metabolism.

2.2. Instrumental Neutron Activation Analysis (INAA)

INAA is a technique for qualitative and quantitative multi-element analysis of major, minor, trace and rare elements in all kind of materials including those from human origin such as blood, nails, hairs and tissue samples [6]. The method is based on the bombardment of a sample with neutrons followed by capture of a neutron by the nucleus of an element and subsequent conversion to a radioactive isotope. NAA requires a source of neutrons, ideally a nuclear reactor, which uses uranium fission to provide a high neutron flux. The type of neutrons generated are of relatively low kinetic energy (KE), typically less than 0.5 eV, and are termed thermal neutrons. However experimental parameters can be varied resulting in neutrons with a moderate (0.5eV-0.5MeV) or high (>0.5MeV) kinetic energy. During this irradiation process, a thermal neutron can be captured by a target nucleus of an isotope of an element resulting in a compound nucleus. This compound nucleus will almost immediately de-excite into a more stable configuration through the emission of one or more characteristic prompt gamma photons. In most cases, this more stable configuration yields a radioactive nucleus. The newly formed radioactive nucleus now typically decays by the emission of a beta particle and one or more characteristic delayed gamma photons. This decay process acts at a much slower rate than the initial de-excitation and depends on the unique half-life of the radioactive nucleus (figure 1). The radioactive emission characteristics and decay paths of the various isotopes are well known. They are usually measured with a semiconductor detector utilizing the semiconducting element germanium. The intensity of the radioactive emissions is proportional to the number of nuclei of the element and based on the information of the spectra of emissions, concentrations of elements, present in the sample, can be calculated. Until the introduction of particle-induced x-ray emission (PIXE), inductively coupled plasma atomic emission spectroscopy (ICP-AES) and inductively coupled plasma mass spectrometry (ICP-MS), INAA was the standard analytical method for performing multi-element analyses with minimum detection limits in the sub-ppm range. The technique is non-destructive, the chemical structures of the sample stay intact, and there is no need to convert and/or dilute a sample into a suitable solution prior to analysis with inherent risks of contamination and element loss. It is a highly accurate technique meeting the requirements of a primary method of measurement. Drawbacks , however, are the remaining radioactivity in the irradiated samples requiring handling and disposal protocols, and the availability of research reactor facilities, which showed a decline over the last years. This may explain why its use in clinical medical research has been limited while a lot of progress has been made in mass spectrometric techniques, which also have easier access. Furthermore not all elements relevant in biological processes, such as nitrogen, carbon and oxygen, can be measured; INAA can detect up to 74 elements. Heavier elements are more likely to be activated and some nuclei can capture neutrons and remain relatively stable, not undergoing transmutation or decay for many months or even years.

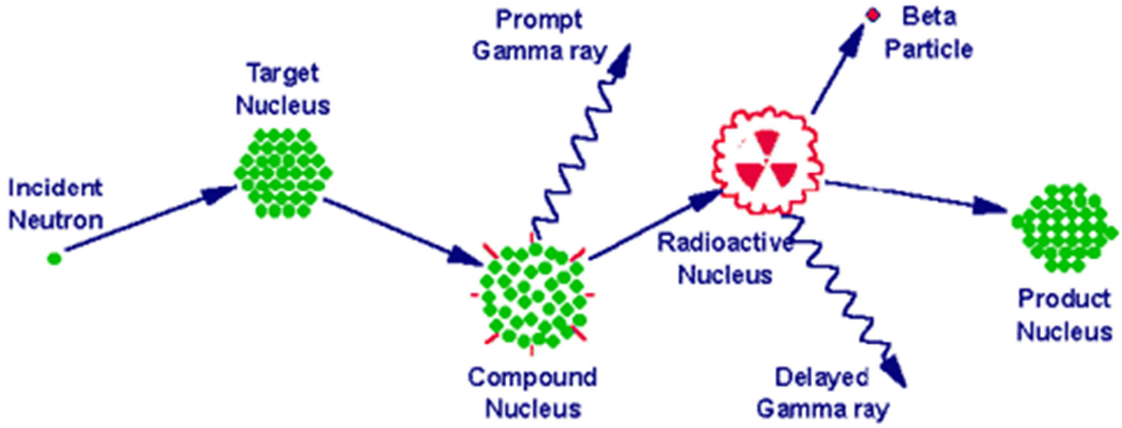

Figure 1. *Neutron activation analysis.*

Like most other techniques, conventional INAA deals with small samples (100 milligrams), but in contrast to those techniques INAA can also handle large samples up to kilograms [7]. This is especially important when an element is not distributed homogeneously in the material to be analyzed or when homogenization procedures fail. The applicability of this so-called large sample INAA has recently been demonstrated in the measurement of iron concentrations in commercially available microwave meals and in porridge fine wheat grain [8]. This makes INAA a very attractive technique in mass balance studies, since not only complete meals can be analyzed reliably but also blood, urine and feces.

Apart from research in food, nutrition, and forensic medicine using hair and nails, INAA has been applied on a wider scale in biomonitoring in which the body burden of toxic chemical compounds and elements in biological substances is measured. Biomonitoring of atmospheric elements is based on the use of organisms that are able to absorb and retain these elements in their tissues. Such organisms can reflect the deposition of atmospheric elements at a certain place as well as its biological impact in the organism itself [9, 10]. Lichens, stable synergistic organisms arising from algae or cyanobacteria living among filaments of fungi, have been extensively used for the evaluation of anthropogenic pollution (urban and industrial). The fact that lichens do not possess roots and cuticles, explains their major dependence on atmospheric sources of nutrients. For biomonitoring both native lichens (passive monitoring) as well as transplanted lichens (active monitoring) can be applied. This form of biomonitoring has been proven useful to register pollution in the proximity of industry but also in the measurement of elements transported by air mass over a large distance [11].

2.3. Enriched Stable Isotopes

Because of their ability to emit radiation, and therefore allow detection, radionuclides have been used and are still used as tracers in medicine. Applications include measurement of survival and half-life times of blood cells, detection of blood loss and studies on the metabolic fate of metals and trace elements. For instance the radioactive Fe-59 isotope has been used to study iron metabolism in both physiologic and pathologic conditions. The major draw-back however is the side effect of radiation, which can cause damage to cells and tissues limiting its use in clinical practice especially in specific groups such as children and pregnant women. An attractive alternative is the use of an enriched stable isotope, especially when the natural occurrence of that isotope is low. By several techniques, such as centrifugation, the isotope can be enriched to concentrations over 90%. After administration of this enriched element, its presence and concentration, when corrected for its low natural presence, reflect the fate of the given dose. In recent years this technique has been especially applied in food and nutritional research analyzing the effect of supplementation and fortification of food with essential elements such as iron and zinc [12]. Although this approach lacks the side effect of radiation its main limitation is the necessity of a measurement technique able to measure at isotopic level. Apart from advanced forms of mass spectrometry, INAA meets these requirements. Recently studies with the enriched stable Fe-58 isotope and INAA have been introduced in clinical studies on iron metabolism [13].

3. Conclusions

A nuclear reactor is not just a provider of energy but can also be used for medical and environmental research. Apart from the production of radionuclides, which have become routine tools in modern diagnostic and therapeutic medicine, the neutron flux of a research reactor allows the measurement of a broad spectrum of elements playing a vital role in biological processes. Neutron activation analysis is a very precise technique of multi-element analysis that can be a welcome addition or adequate alternative to other techniques, that can measure on isotopic level. Attractive properties of the technique include its non-destructive character of samples, simple preparation of samples without risk of contamination and the availability to measure large samples up to kilograms, which is especially of interest in case of problems with homogenization. Not only can elements be measured in all kind of biomaterials but the use of enriched stable isotopes allows in vivo studies of trace element kinetics without the side effect of radiation. Since the number of research reactors is limited, access to its facilities can be problematic. However, in many research reactor facilities collaboration with clinical researchers will be encouraged.

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