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The study of *in vivo* quantification of aluminum (Al) in human bone with a compact DD generator-based neutron activation analysis (NAA) system

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Abstract

The feasibility and methodology of using a compact DD generator-based neutron activation analysis system to measure aluminum in hand bone has been investigated. Monte Carlo simulations were used to simulate the moderator, reflector, and shielding assembly and to estimate the radiation dose. A high purity germanium (HPGe) detector was used to detect the Al gamma ray signals. The minimum detectable limit (MDL) was found to be 11.13 μg g^{-1} dry bone (ppm). An additional HPGe detector would improve the MDL by a factor of 1.4, to 7.9 ppm. The equivalent dose delivered to the irradiated hand was calculated by Monte Carlo to be 11.9 mSv. *In vivo* bone aluminum measurement with the DD generator was found to be feasible among general population with an acceptable dose to the subject.

Keywords

aluminum; neutron activation analysis; neutron generator

Introduction

Aluminum is known to be the third most abundant element on earth. Although it is present throughout the natural environment, there have yet to be any inherent biological functions in the human body discovered. Given its ubiquity in the environment, humans are continually exposed to aluminum. In addition to exposures that occur naturally during the course of life, we are exposed to aluminum-based deodorants, aluminum containing antacids, through occupational processes, and from medical conditions (Yokel and McNamara 2001). The human body has the ability to handle intakes of aluminum that typically are encountered by healthy individuals on a day to day basis, thus maintaining a body burden that is much less than one gram in the total body (ICRP 1975). However, when people are exposed to excessive amounts of aluminum or if they are medically compromised, it is possible that

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Declaration of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

intakes of aluminum may be greater than the body's ability to excrete it. Aluminum buildup above normal levels has been observed in occupationally exposed groups of workers involved in aluminum processing as well as welding operations (Sjögren *et al* 1983, Elinder *et al* 1991). Buildup has also been documented in individuals medically exposed to aluminum via treatments for end stage renal disease (Elinder *et al* 1991, Cannata-Andía 2001, Cannata-Andía and Fernández-Martín 2002). The experiences gathered from medically compromised individuals who were exposed to high levels of aluminum led to the recognition that large scale incorporation of the element into the skeleton is possible. A buildup of aluminum in the individual or worker may lead to a variety of disease states affecting the skeletal, nervous, and hematopoietic system. Aluminum was determined to be able to cause encephalopathy, osteomalacia, and microcytic anemia in patients undergoing dialysis (Becaria *et al* 2002, Malluche 2002). Extending these possibilities to those exposed occupationally, aluminum concentrations in bodily tissues above normal levels have been identified in workers engaged in processes involving the element (Priest 2004).

A study published by Fraga *et al* described the neurological damage associated with increased levels of Al. Aluminum intoxication increases production in the brain of 2-thiobarbituric acid reactive substances (TBARS), which enhance lipid peroxidation (Fraga *et al* 1990). Another study in 1992 showed humans and animals that were exposed to aluminum demonstrated a syndrome characterized by impairment, depression, and poor memory (White *et al* 1992). Also, the relation between aluminum and Alzheimer's disease remains a possible, yet controversial subject. Previous studies have shown an increased risk of Alzheimer's disease in regions with high levels of aluminum in drinking water (Martyn *et al* 1989, McLachan *et al* 1991, O'Mahony *et al* 1995).

Given the potential health implications that can arise from an accumulation of aluminum and its ubiquitous presence in both the environment and a variety of industrial settings, a reliable biomarker to assess cumulative aluminum exposure is significant. Often, aluminum is quantified in blood or urine samples. It has been found that aluminum levels are increased in serum and urine of people who are exposed occupationally (Gitelman 1995, Gitelman *et al* 1995). Also, a study demonstrated high levels of aluminum in the urine and plasma of pre-mature infants (Sedman *et al* 1985). Unfortunately, aluminum concentrations in bodily fluids are highly variable and influenced by exposure time, the individual's metabolic rate, and other specific factors such as the route of exposure and exposure conditions (Sedman *et al* 1985). Measuring what is present in bodily fluids may not be an accurate description of what is of concern, that is, the individual's cumulative exposure to aluminum. Long term accumulation of aluminum in the body largely occurs in the skeletal system (Yokel *et al* 2001). Aluminum incorporated in the skeleton may remain with a very long residence time, as the turnover in bone is on the order of years (Yokel *et al* 2001). To evaluate the potential for negative long term effects from an exposure, it would be more appropriate to determine how much aluminum is being retained in bone, not how much is circulating in blood at a given instant or how much is currently being excreted. Quantification of aluminum in bone could be used to indicate exposures to aluminum and whether medical intervention is warranted.

One of the non-invasive techniques used to identify and quantify elements in various samples is neutron activation analysis (NAA). NAA is a mature technique that has been used in the past to quantify aluminum as well as to evaluate the presence of various elements in bone (Pejović-Milić *et al* 1998, Davis *et al* 2008, Mostafaei *et al* 2015b). The nuclei present in a sample are irradiated by neutrons, in our case, the neutrons produced by a deuterium-deuterium (DD) generator and optimized by a moderator/reflector/shielding assembly. A portion of the irradiated nuclei will absorb neutrons, resulting in an activated or unstable state. In a move to attain stability, the nuclei will decay, followed by the emission of excess energy in the form of gamma rays. These gamma rays can be detected and used to identify the isotopes that originally emitted them, based on their energy. In addition, the mass of the substance that emitted them may be quantified by comparing the signals with those from calibration standards. Currently, our group is working on optimizing a method to quantify aluminum in bone via NAA, utilizing a tabletop neutron generator (NG). Fairly recently, such generators have become commercially available, allowing the generation of neutrons with a relatively small, movable piece of equipment. Aluminum is measured via the ^{27}Al(n, γ)^{28}Al reaction. ^{28}Al beta decays to ^{28}Si, followed by the emission of a gamma ray with energy of 1.78 MeV. The aluminum half-life and thermal cross section are 2.25 min and 0.23 barns respectively. Aluminum-28 can also be produced via the ^{31}P(n, α)^{28}Al reaction. Of particular concern is this reaction with phosphorus, which is a major component of bone. Fortunately, at the neutron energies produced by the DD generator (2.45 MeV), the cross section of the reaction is null, meaning the production of ^{28}Al through the ^{31}P reaction is not probable (Gatschk *et al* 1980). As can be seen in figure 1 the neutron cross section for ^{28}Al at 2.45 MeV is almost zero. The neutron cross section at 2.6 MeV is 3.89×10^{-17} barns, meaning the ^{31}P(n, α)^{28}Al reaction is not likely to occur (JEFF 3.2).

Using these data, the ultimate goal of our study is to develop a transportable system that can accurately evaluate *in vivo* skeletal loads of aluminum, with minimal inconvenience and radiation dose to the research subject.

Methods and materials

Monte Carlo simulation

The Monte Carlo N-Particle (MCNPX) code, version 2.7.0, developed by Los Alamos National Laboratory (LANL) was used in this study. MCNPX is a well-established Monte Carlo code that can simulate neutron and photon interactions with matter (http://mcnp.lanl.gov/). The latest cross-sectional data, which allows the user to tally neutron fluxes, activation, and radiation dose, is included in the MCNPX code. To compute the neutron fluence spectrum for a hand the F4 tally was chosen. Two F6 tallies were used, one to compute the neutron dose and a second to compute the photon dose. The number of tracked particles was always set at 10^{10}, with the neutron source modeled as an isotropic point source. A human hand, composed of soft tissue and cortical bone, was also simulated in the code, according to elemental compositions specified by ICRU 44 and ICRP 70 (ICRU 1989, ICRP 1995). The hand was modeled as a rectangular parallelpiped with dimensions 12 cm × 10 cm × 1.5 cm. A quantity of aluminum was added to the simulated hand model and the amount of ^{28}Al produced by neutron absorption was determined by the code. The

influence of altering the geometry of the moderator on the amount of ^{28}Al produced was calculated and the system optimized such that the greatest amount of signal could be produced with an acceptable radiation dose to a human subject. Different materials were also evaluated as they each moderate, reflect, and shield neutrons to varying degrees. In order to find the best moderator, reflector, and shielding material, graphite, paraffin, water and polyethylene were analyzed by Monte Carlo simulation.

Compact deuterium-deuterium (DD) neutron generator

The performance of NAA was carried out with a customized table-top DD neutron generator, model DD-109M, manufactured by Adelphi Technology, Inc. (Redwood City, CA). The generator creates plasma of positively charged deuterium ions by means of radiofrequency induction. The plasma is then electrically accelerated towards a negatively biased (nominally −120 kV) titanium target, interacting and creating titanium hydride. As more deuterium impinges on the deuterium hydride, deuterium-deuterium (DD) reactions begin to occur, resulting in the production of 2.45 MeV neutrons by way of (IAEA 2012):

$$^{2}\mathrm{H}+^{2}\mathrm{H} \rightarrow {}^{3}\mathrm{He} + \text{neutron} + Q(=3.29\,\mathrm{MeV})$$

The generator is able to produce a neutron flux of about 7×10^{8} neutrons per second, using an ion current of about 12 mA, operated at a bias of 120 kV. The neutrons emerge from the generator essentially mono-energetically, with 2.45 MeV of kinetic energy. The characteristics of the DD neutron generator are described in our previous studies (Liu *et al* 2013, 2014, Mostafaei *et al* 2015a).

Al-doped phantoms

A series of phantoms were constructed in 50 ml plastic tubes containing 30 ml distilled deionized water and aluminum of varying amounts. The aluminum was in the form of aluminum nitrate $Al(NO_3)_3$, which is soluble in water. Each phantom consisted of deionized water to which was dissolved 0.01 g aluminum, 0.02 g aluminum or 0.03 g aluminum. A blank phantom was produced that contained only deionized water with no aluminum added.

HPGe detector and gamma ray spectrum analysis

In this study, a high-purity germanium (HPGe) detector (GMX90P4-ST, 100% efficiency) was used as a detection system. Gamma rays were collected by the detector and processed by a digital signal analyzer (Ortec DSPEC Plus). The Maestro multichannel analyzer (MCA) (Ortec, model A65-B32) was used, to sort and plot acquired photons according to their energy. The Levenberg-Marquardt fitting algorithm was used for curve fitting and the analysis was programmed by Matlab. We used an automated routine that was developed in-house to calibrate acquired spectra from irradiation samples to a source that contained long-live radioactive isotopes whose identities and primary gamma ray emissions were well characterized. The routine was used to identify counts from the 1.78 MeV gamma-rays from Al activation and gamma-rays from the activation of other elements.

Irradiation, decay, and counting time

The system has been constructed in order to irradiate human subjects, with the goal of assaying skeletal aluminum burdens. The research subject will place a hand in the irradiation chamber close to the generator. The remainder of the subject's body will be shielded from the majority of the neutrons. Technically, the system will therefore assay the amount of aluminum in the subject's hand, as a representative sample for the skeletal aluminum load. One parameter that was verified was the determination of an ideal length of irradiation. As a substance is irradiated, the number of activated atoms produced increases exponentially, eventually reaching an asymptote as the rate of production nears the rate of decay of activated atoms. This relationship is well known and is mathematically described by: Activity = $\varphi\sigma N(1 - e^{-\lambda t})$ where; φ is the neutron flux density at the sample, σ is the interaction cross section, N is the number of present target atoms, λ is the physical decay constant of the activated atoms, t is the irradiation time.

As the irradiation time is increased, the radiation dose to the subject will linearly increase while the continued production of activated atoms for analysis will be produced at an increasingly lower rate as the asymptote is approached. Table 1 shows possible activities in a sample with different irradiation time.

From the activation activity relationship, which we verified by measurement, it was deter mined that an irradiation period of 300 s was to be utilized. This period allows for the production of approximately 79% of the possible activity in a sample. Irradiations greater than this in length would result in much greater radiation doses to subjects with minimal increases in the amount of activated atoms to analyze. Since the half-life of Al-28 is only 2.25 min, the time between the end of the irradiation and the beginning of the counting is made as short as practically possible. The transferring time was chosen to be 45 s.

An additional consideration to the setup of the system is the length of time that a sample is to be analyzed. Similar to irradiation time, as counting times are increased, the detected signal increases exponentially towards an asymptote. The downside to using exceedingly long count times is that the analysis system can only work with one subject at a time and the research subject will not want to be subjected to an excessively long process, especially if the increase in garnered information is limited as the asymptote is approached. The counting time of 300 s, which allows the recovery of approximately 79% of the available information, was chosen for measurements.

Results

Monte Carlo simulation of the moderator/reflector/shielding system

The generator was modeled in MCNPX using manufacturer supplied schematics. During the course of the optimization, a variety of materials were considered for the moderator including graphite, paraffin, water, and polyethylene. It was found that the differences among the materials on sample activation in the irradiation cavity were not large and high density polyethylene was selected for its simplicity of use. The optimal moderator dimensions for activation were determined by simulation and a thickness of 5 cm of polyethylene was placed in the irradiation cavity between the generator and irradiation

samples. Eight centimeters of graphite was chosen and simulated as a reflector to scatter neutrons back towards the cavity. For shielding, 15 cm of high density polyethylene with 5 cm of borated polyethylene was selected and simulated (Liu *et al* 2014, Mostafaei *et al* 2015a). The cross section of the irradiation cavity is shown in figure 2.

Data collection and system detection limit

Each of the four phantoms was irradiated by the DD generator for a period of 300 s. Following irradiation, the contents of the phantom were transferred to a non-irradiated plastic tube and placed in front of the HPGe detector for counting. Transfer to a non-irradiated plastic tube was done to limit the influence of aluminum present not in the phantom but in the plastic container. A total of 45 s was given for transferring the sample and placing it in the counting chamber, after which counting began. Counting of the sample was carried out for a period of 300 s. The spectral shape can be seen in figure 3.

To validate the acquired counts from experiments with MCNPX, the number of Al counts from the phantoms with different Al masses (0.01, 0.02 and 0.03 g) obtained from the simulation was calculated as: Number of counts = $R \times N \times \varepsilon \times \theta \times F \times S \times D \times C$

Where, R is the reaction rate, N is the number of atoms for the target nuclide, ε is the detector efficiency (0.018 for ^{28}Al γ-ray energy at 1.78 MeV when the sample was placed in front of the detector window), θ is the branch ratio of the characteristic γ-ray for the specific radio-nuclides produced, F is the neutron flux per second, S is the saturation factor, D is the decay factor, and C is the counting factor.

All the simulation results have relative uncertainties of less than 5%. As can be seen from table 2 the number of counts calculated from experiments and Monte Carlo simulations were significantly different (in average by factor of 2.6), and the reason will be discussed in the next section. The Al phantom calibration lines using experiment results are shown in figure 4.

The results of background counts for the 1.78 MeV gamma ray that were fitted in Matlab yielded 4.1 counts. The minimum detection limit (MDL) of the system is calculated by $\text{MDL} = \frac{2 \times \sqrt{\text{background}}}{\text{slope}}$. Using the fitted background and the slope of the calibration line determined in figure 4, an MDL of 579.47 micrograms of aluminum is calculated. If the aluminum was incorporated in an irradiated hand, which has a skeletal mass of 52.1 g (ICRP 1995), a detection capability of this system of 11.13 μg Al g^{-1} dry bone (11.13 ppm) is inferred.

Radiation dose

MCNPX was used to model the radiation doses that could be received by potential research subjects. Using a simulated hand, the radiation dose (equivalent dose, according to ICRP 60 weighting factors) due to both the neutron as well as photon dose components was modeled. Given an irradiation time of 5 min with neutron flux of 7×10^8 n s^{-1}, the equivalent dose to the hand was found to be 11.9 mSv. Recent work on dosimetry for this system reported a measured equivalent dose of 35.9 mSv from neutrons and photons to an extremity from a 10

min irradiation (Sowers 2015, Sowers *et al* 2015). Since the dose is constant with time, a 5 min irradiation would result in an extremity equivalent dose of 18.0 mSv. The combined neutron and photon radiation dose outside the irradiation cavity that would be received by an individual undergoing study would be equal to an equivalent dose of 8.5 μSv for a 5 min irradiation.

Overall, the radiation dose to the hand and to the whole body is acceptable. The dose to the hand is less than 1/10 of the annual dose limit to the extremities for occupational workers (500 mSv). The whole body effective dose is much lower than that from a standard AP chest x-ray (100 μSv), and annual background radiation (3000 μSv) (ICRP 1991).

Discussions

This application of a DD generator-based NAA technique is important in three aspects. First, a table top neutron generator is a system that can be transported out of a fixed laboratory environment to distant sites of interest for performing analysis. In the past, the majority of NAA had been performed with either large accelerator systems or nuclear reactors, both of which are immobile. The eventual use of this application of the NAA technique will be to measure skeletal aluminum loads in humans, especially workers who have been occupationally exposed to aluminum and other metals. With an immobile source of neutrons, the research subjects must be brought to the irradiation facility for analysis, which would be very expensive and logistically difficult for the study of large numbers of people. The table top neutron generator and detection equipment used herein can be shipped proximate to those under study, thereby reducing overall costs and allowing the inclusion of larger groups of people into studies.

Secondly, the energy of the neutrons produced by the DD reaction is less than deuterium-tritium (DT) neutron generators and some larger accelerators. The presence of higher energy neutrons lead to non-desirous nuclear reactions being possible, all of which negatively affect the useful analysis signal. Nuclear reactions are energy dependent and interacting particles must have energies greater than the threshold for a specific reaction to occur. DD generators produce neutrons with lower energies than many other sources, thereby precluding a number of nuclear reactions which would negatively affect the analysis.

The third unique aspect of this system is the use of high efficiency HPGe detector. While such detectors are relatively expensive compared to those utilizing scintillators such as sodium iodide, they offer superb energy resolution with similar absolute efficiency for medium energy γ-rays. Compared to sodium iodide detectors which have an energy resolution of about 10% at 661.62 keV, the HPGe detector in this study has an energy resolution of about 0.3%. The superior energy resolution is important in maintaining low background under the peak of interest and hence significantly reducing the MDL of the system. In addition, in a situation such as performing NAA *in vivo* where a large variety of isotopes may be present, the HPGe detector will give confidence in the ability to count only those photons arising from isotopes of interest such as ^{28}Al and ^{49}Ca (reducing peak interferences).

Using the NAA setup in our laboratory, we were able to detect an amount of aluminum down to 11.13 ppm, which is comparable to the skeletal aluminum loads of 10.6 ppm reported in the literature for normal human subjects (Priest 2004). An additional high efficiency HPGe detector can improve the MDL to 7.9 ppm (factor of $\sqrt{2}$). It must be noted that the aluminum detection capability of our system was quantified in small, water-based phantoms. While the combination of the energies of the neutrons generated by the system and the excellent energy resolution of the high purity germanium detector limits the amount of inference present in the system, more realistic phantoms will need to be experimented with to confirm the detection limit. The aluminum must be detected in a matrix that more closely resembles the elemental composition of bone and in physical dimensions similar to those of a human hand.

NAA of aluminum has been performed by others, albeit with slightly different systems. Aslam Davis *et al* (2009) utilized neutrons generated from the ^{7}Li(p, n) ^{7}Be reaction produced in a Tandetron linear accelerator to activate aluminum. Gamma rays were detected with an array of nine NaI(Tl) detectors, resulting in a detection limit of 290 micrograms of aluminum in calibration standards. We measured a detection limit in calibration standards of 579 μg of aluminum using a single HPGe detector. Increasing the number of detectors in our system along with optimization of the detection process should lower the detection limit nearer to that previously attained by fixed irradiation facilities.

It was recognized that aluminum is essentially present in all materials. To reduce contamination, phantoms using distilled ‘non-contaminated’ water were made. However, aluminum could still be present in the distilled water phantom. Another consideration that was evaluated was the prevalence of aluminum in the environment and its ability to be a confounding contaminant in samples under evaluation. Aluminum is the third most common element on earth and nearly everything comes in contact with aluminum at some point. Given that we are analyzing individual atoms, even casual contact during manufacturing or processing of samples can result in detectable aluminum contamination. As such, we irradiated a number of items that were not exposed to aluminum to determine if we could detect contamination. The results are shown in table 3.

As can be seen from table 3, aluminum is almost everywhere. To reduce the amount of Al in the plastic vial that was used in this study as a container, the phantom materials were transferred to a non-irradiated container. However, that did not eliminate aluminum contamination in the phantoms, as can be seen in the results shown above. Therefore one challenge of further study is to make a set of aluminum-free phantoms for an accurate calibration. A study conducted by Mostafaei *et al* found an aluminum-free material, which can be used as a binder to make a solid phantom (Mostafaei *et al* 2013). Using materials with minimal or no aluminum contamination in the bone phantoms for the system calibration is essential. However, for *in vivo* measurements, aluminum contamination will be less an issue, since the participants will be asked to clean their hand and arm before the measurement.

Although the HPGe detector was shielded with lead bricks and was placed far from the DD generator, contamination was still observed from the activation of the Al in the surrounding

area (including the detector itself). For future study, reducing the background by locating the detection system further from the DD system while keeping transferring time as short as possible is essential.

The number of counts obtained from the MC simulation and from the experiment differed by a factor of about 2.6. There are several potential causes for this difference, most significantly related to inaccuracies in the simulations. There were slight geometrical discrepancies between the simulation of the water based phantom and its physical reality. Additionally, the detector efficiency was measured with a mixed-isotope gamma ray standard whose geometry differed slightly from that of the phantom. A second cause of differences was the actual operation of the irradiator itself. Due to a lack of knowledge of the angular distribution of neutron production in the irradiator, the source of neutrons was modeled as a simple isotropic point source. The difference between the true and simulated neutron source affects the flux distribution in the irradiation cavity. Secondly, a neutron flux of 7×10^8 neutrons per second was used to calculate the number of counts obtained from MC simulation. This flux could be slightly higher and fluctuate to a degree during the course of the experiments. We are still working on the ways to determine the exact real time neutron flux and to normalize measurements for potential variations during irradiation. Nevertheless, the results obtained from the experiments should be trusted here.

Conclusion

This study involved the development of a neutron activation analysis (NAA) system to measure aluminum present in human bone. The development of a table top deuterium-deuterium (DD) neutron generator based NAA system to measure aluminum in human bone (*in vivo*) was achieved. The system was able to attain sensitivity for aluminum sufficient to measure skeletal aluminum loads in normal human subjects. The aluminum MDL was found to be 11.13 ppm, which can be reduced to 7.95 ppm with two HPGe detectors. The system should therefore be able to differentiate between normal and elevated human skeletal aluminum loads, via *in vivo* measurements.

Acknowledgments

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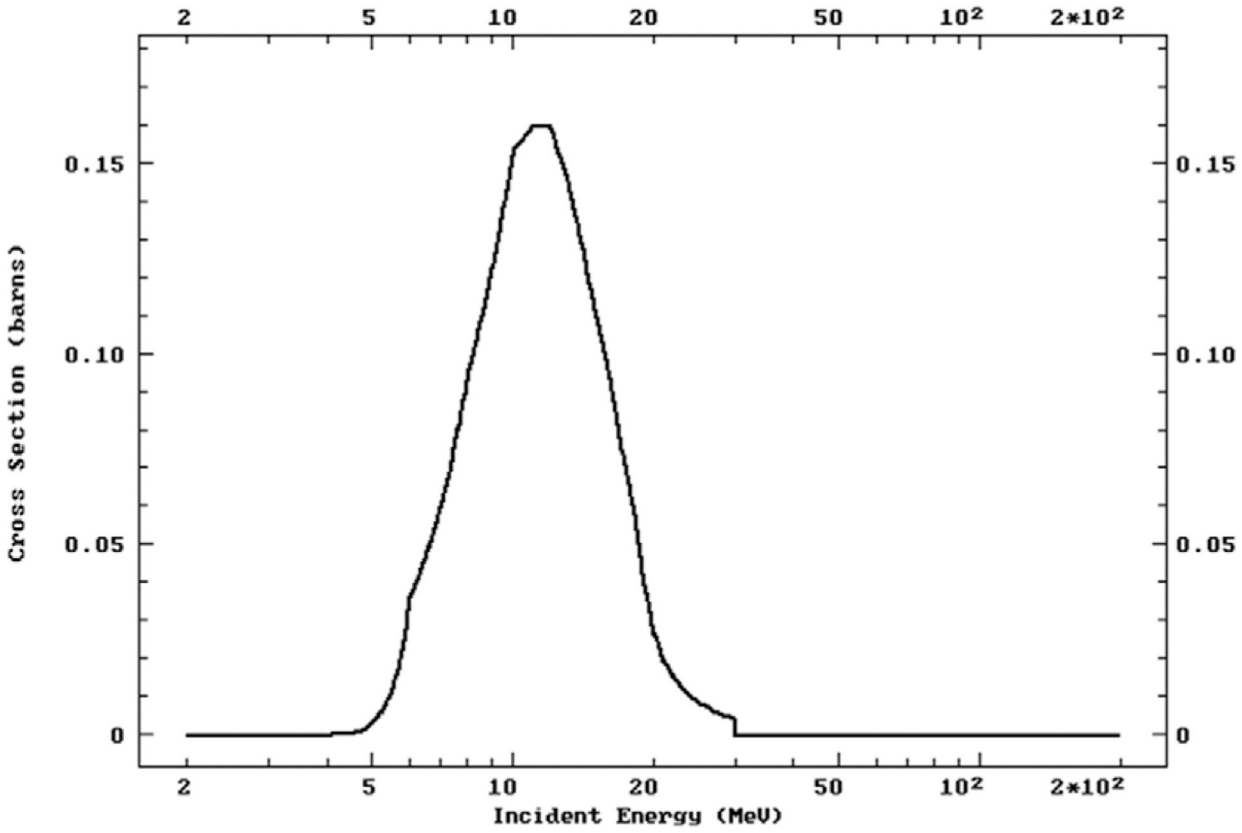

Figure 1.
The cross-section of the $^{31}P(n,\alpha)^{28}Al$ reaction (JEFF 3.2).

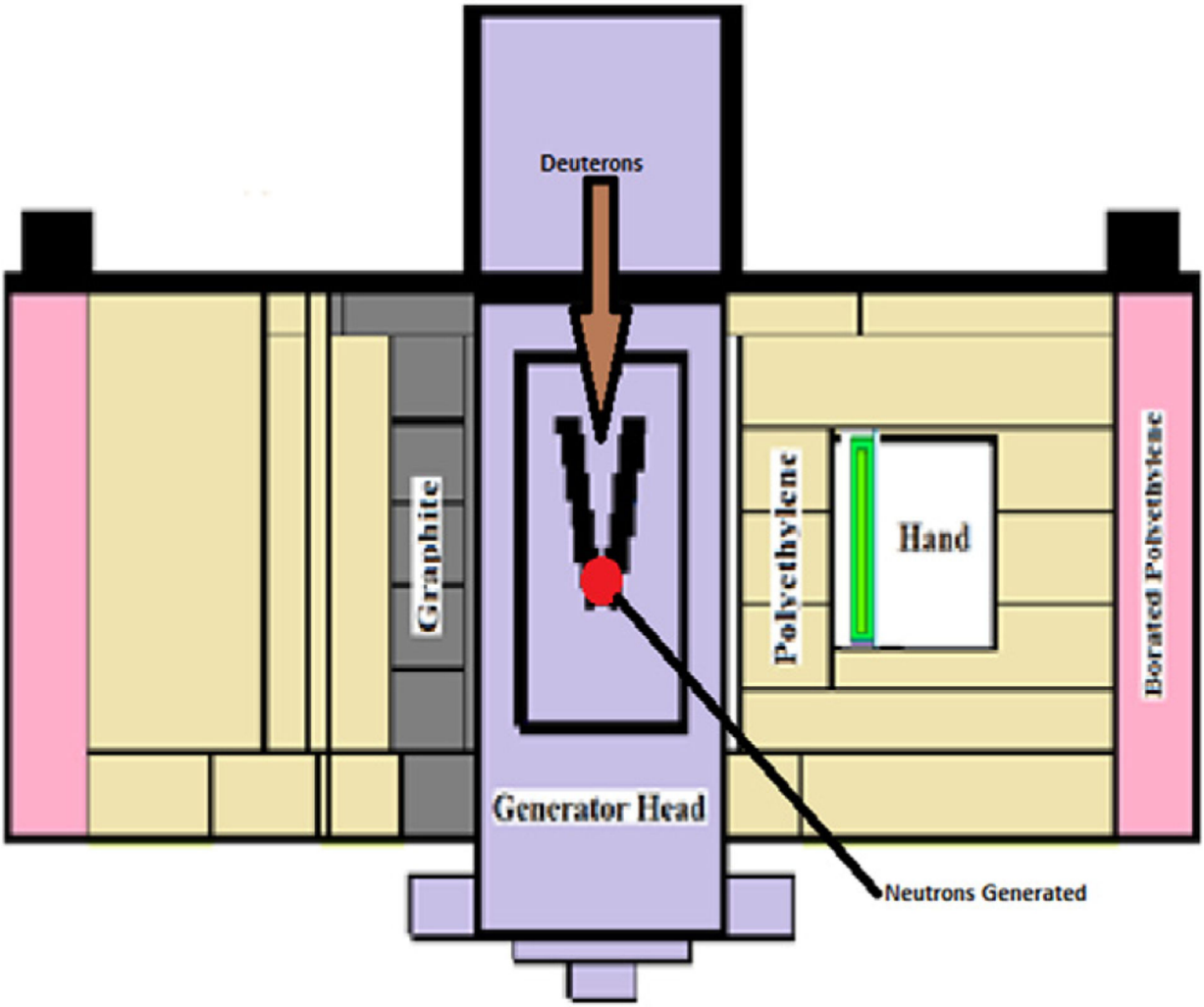

Figure 2.
Cross section of the irradiation cavity.

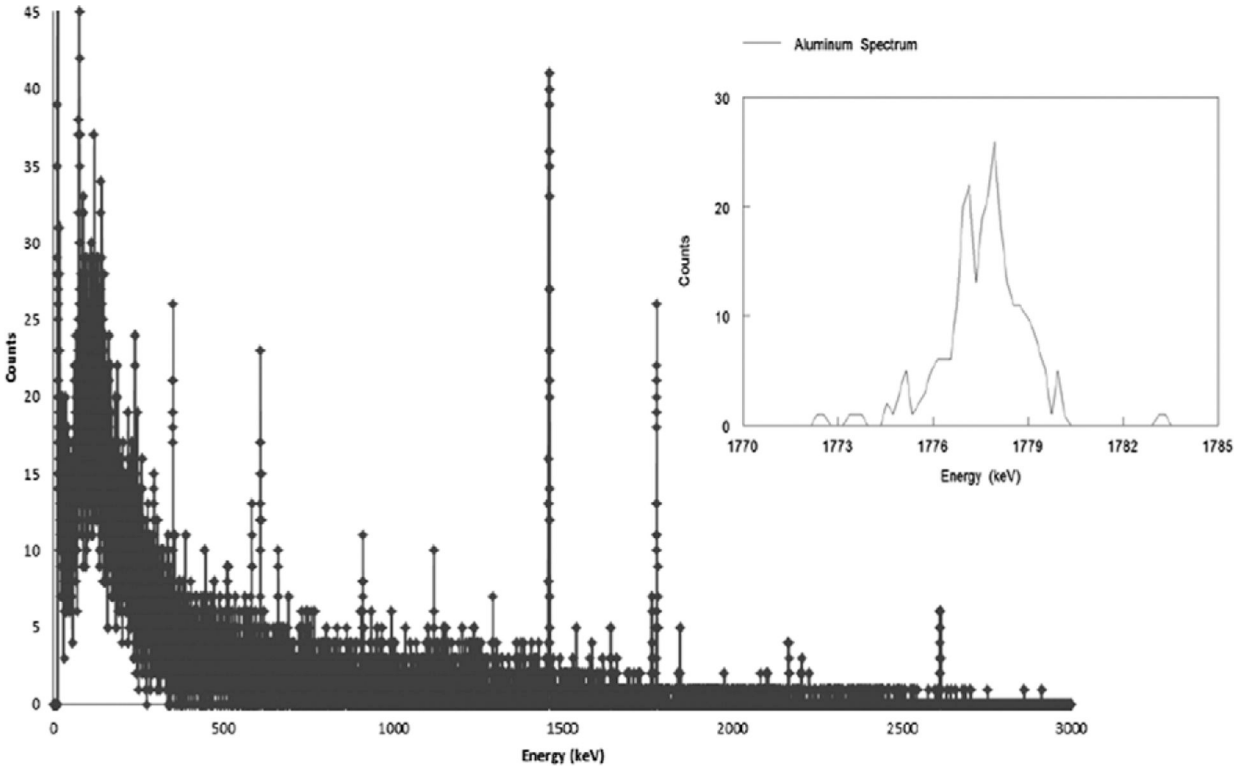

Figure 3.
Spectra from 0.03 g of Al.

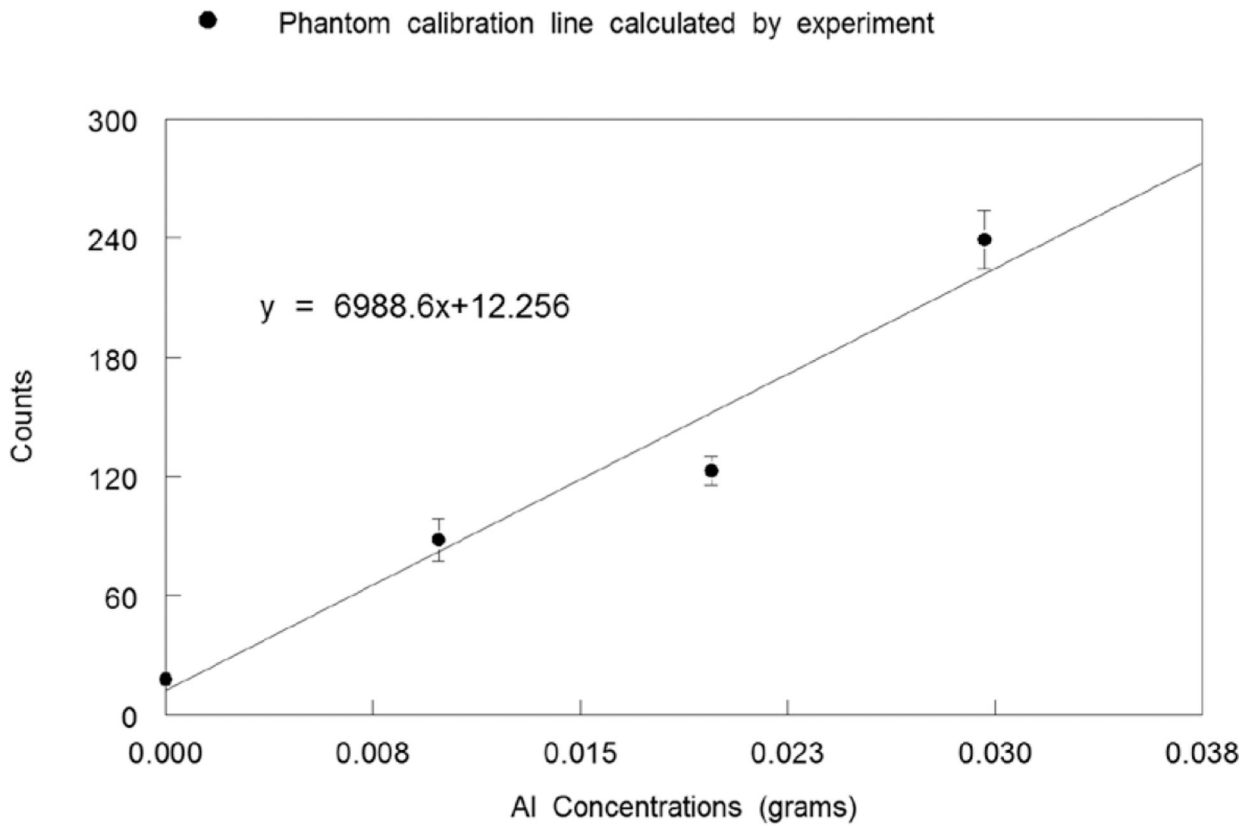

Figure 4.
Phantom calibration lines obtained from two detectors.

Table 1.

Percentage of activation activity with different irradiation time.

Irradiation time (s)	Percentage of activation activity
100	40.27
200	64.32
400	87.27
600	95.46
800	98.38
1000	99.42

Table 2.

Number of counts calculated by experiments and MCNPX.

Amount of aluminum (g)	Acquired counts from experiments	Acquired counts from MCNPX
0	17.9 ± 4.1	0
0.01	88.2 ± 10.6	29.1 ± 0.5
0.02	122.9 ± 7.5	59.9 ± 1.4
0.03	239.3 ± 14.7	89.9 ± 1.8

Table 3.

Analyze different materials to test aluminum contamination.

Material analyzed	Counts in aluminum peak
Background (no sample)	4 ± 2
30 ml deionized water in plastic vial	24 ± 4.9
Glass vial	205 ± 14.3
Small plastic bag	28 ± 5.3
Small plastic vial (no water)	22 ± 4.7
Piece of 11″ × 8.5″ paper	32 ± 5.7