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A neutron activation technique for manganese measurements in humans

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ABSTRACT

Manganese (Mn) is an essential element for humans, animals, and plants and is required for growth, development, and maintenance of health. Studies show that Mn metabolism is similar to that of iron, therefore, increased Mn levels in humans could interfere with the absorption of dietary iron leading to anemia. Also, excess exposure to Mn dust, leads to nervous system disorders similar to Parkinson's disease. Higher exposure to Mn is essentially related to industrial pollution. Thus, there is a benefit in developing a clean non-invasive technique for monitoring such increased levels of Mn in order to understand the risk of disease and development of appropriate treatments.

To this end, the feasibility of Mn measurements with their minimum detection limits (MDL) has been reported earlier from the McMaster group. This work presents improvement to Mn assessment using an upgraded system and optimized times of irradiation and counting for induced gamma activity of Mn. The technique utilizes the high proton current Tandetron accelerator producing neutrons *via* the $^{7}Li(p,n)^{7}Be$ reaction at McMaster University and an array of nine NaI (Tl) detectors in a 4π geometry for delayed counting of gamma rays. The neutron irradiation of a set of phantoms was performed with protocols having different proton energy, current and time of irradiation. The improved MDLs estimated using the upgraded set up and constrained timings are reported as 0.67 μgMn/gCa for 2.3 MeV protons and 0.71 μgMn/gCa for 2.0 MeV protons. These are a factor of about 2.3 times better than previous measurements done at McMaster University using the *in vivo* set-up. Also, because of lower dose-equivalent and a relatively close MDL, the combination of: 2.0 MeV; 300 μA; 3 min protocol is recommended as compared to 2.3 MeV; 400 μA; 45 s protocol for further measurements of Mn *in vivo*.

Introduction

Manganese is a trace element that is an essential nutrient for normal development and body function across the life span of all living organisms [1]. In humans, the diet is the main source of Mn, with an adequate intake of 2–4 mg/day and an upper tolerable intake of 11 mg/day for total Mn intake [2]. The major storage of Mn is in the bones (about 50%) and its excretion is through the liver [3]. A healthy person with normal liver and kidney function can excrete excess dietary manganese. Inhaled Mn is of greater concern because it can bypass the body's normal defense mechanisms; *i.e.* it is often transported directly to the brain *via* olfactory nerve [4] before it is metabolized by the liver. Also, inhalation exposure to high concentrations of manganese dusts can cause an inflammatory response in the lung, which, over time, can result in impaired lung function.

Manganese is one of the most widely used metals in industry [5]. Exposure to Mn dust occurs primarily in mining, and metallurgical operations for iron, steel, ferrous and nonferrous alloys. Manufacturing of dry-cell batteries, anti-knock gasoline additives, pesticides, pigments for ceramics, dyes, and matches can also lead to occupational Mn exposure. Manganese fumes are produced during metallurgical operations and several types of welding operations. The principal sources of Mn in the atmosphere are however, from natural processes including volcanic gas and dust, and forest fires [6].

Exposure to Mn is usually *via* inhalation, which can lead to Mn accumulation and results in adverse health effects including damage to the lungs, liver, kidney and central nervous system [7,8]. Mn toxicity has been reported through occupational (*e.g.* welder, miner) and dietary over exposure. Prolonged exposure to high Mn concentrations (>1 mg/m^3) in air may lead to a Parkinsonian syndrome known as "manganism" [9–12]. Numerous studies have

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indicated that welders may be at high risk of Parkinson's disease and neurological health effects [9–12].

The majority of the available scientific literature on Mn exposure, body burden and its health effects comes from animal studies and invasive methods like biopsies and autopsies. Toxic elements like Mn are commonly measured in blood and serum, or by a bone biopsy. It is widely accepted that blood and serum concentrations of elements provide information only about the recent exposure to the element, and therefore do not necessarily reflect chronic exposure of an individual. On the other hand, bone biopsy is painful, involves a risk to the patient and it may not be possible to repeat it several times. The assessment of lifetime exposure from the general environment, or the work place, to a toxic element therefore requires a different approach. Because toxic elements like Mn are well retained by bone tissue and may reside there for years to decades, a non-invasive, non-destructive and without-pain neutron activation based diagnostic technique is being developed and used to assess Mn. Taking into account the large accumulation of Mn in bone, an X-ray fluorescence spectroscopy or neutron-based spectroscopy methods are being considered as novel non-invasive tool for assessing Mn exposure and toxicity [13]. However, low energy of Mn X-rays, together with their relatively low fluorescence yield make neutron activation analysis (NAA) the more promising approach. This non-invasive *in vivo* technique can (i) measure Mn amounts in humans, (ii) contribute to limited human data, regarding current knowledge of Mn metabolism and (iii) possibly be helpful in early detection of accumulation resulting from over-exposure in industrial and environmentally exposed populations. Of many different techniques applied *e.g.* atomic absorption spectrometry and inductively coupled plasma atomic emission spectrometry or mass spectrometry to the determination of total Mn content, NAA is a prime example of a non-invasive analytical technique. This method is extremely valuable because of its high specificity and sensitivity for very low concentrations of Mn, as well as several other elements. In contrast to other commonly used techniques, in the case of NAA the sample is not permanently damaged and can be saved for further analysis. The technique is also useful to benchmark the accuracy of results obtained by other analytical methods.

The $^{55}Mn(n,\gamma)^{56}Mn$ reaction is used for the *in vivo* neutron activation analysis (IVNAA) technique. ^{55}Mn, a stable isotope (natural abundance is 100%) undergoes thermal neutron absorption with a high capture cross section of 13.3 barn, producing a radioactive isotope ^{56}Mn, which decays with a half-life ($T_{1/2}$) of 2.58 h, emitting a γ-ray of energy 0.846 MeV having intensity (I_γ) of 98%. The substantial amount of magnesium present in the human body produces ^{27}Mg through the $^{26}Mg(n,\gamma)^{27}Mg$ reaction, which is expected to cause spectral interference, since ^{27}Mg emits a γ-ray of 0.843 MeV with $I_\gamma = 72\%$, close in energy to the γ-ray of ^{56}Mn. However, the difference in half-lives of the two is advantageous in differentiating their contributions as ^{27}Mg is comparatively short lived with a $T_{1/2}$ of 9.46 min. The $^{48}Ca(n,\gamma)^{49}Ca$ reaction is also studied for normalization and quantification, ^{49}Ca decays with a $T_{1/2}$ of 8.7 min and a γ-ray of energy 3.08 MeV with $I_\gamma = 91\%$ [14].

IVNAA of Mn performed using a Tandetron accelerator is based on the neutron production reaction, $^{7}Li(p,n)^{7}Be$. The Q value of the endothermic nuclear reaction is 1.64 MeV and the threshold energy is 1.88 MeV. The possible maximum energies of neutrons from protons of 2 MeV and 2.3 MeV are 0.23 MeV and 0.57 MeV respectively along the beam axis *i.e.* 0° and the total neutron yield from 2.3 MeV protons is 5.25 times that 2.0 MeV protons [15]. Therefore, the maximum energy of neutrons is such that the potentially interfering reactions with iron $^{56}Fe(n,p)^{56}Mn$ ($E_{th} = 2.97$ MeV) and $^{57}Fe(n,d)^{56}Mn$ ($E_{th} = 8.48$ MeV) [14], cannot take place.

The hand bone is chosen for *in vivo* neutron activation because bone tissue has the highest concentration of Mn with approximately 50% of the total body Mn content [3]. In addition, from number of animal studies it is evident that bone is a long term storage site for manganese and to measure a hand bone is technically convenient compared to complexity of using neutron activation method at other sites of body. Also, the effective radiation dose to the subject is much lower when only the hand is exposed to the neutron beam as opposed to a whole body irradiation. Earlier studies done at our laboratory demonstrated the accumulation of Mn in human hand following the inhalation of the element in occupational exposures, and that it is measurable using IVNAA [16–20]. We have conducted a few feasibility tests and measurements on occupational subjects but the levels of Mn in the control subjects were below the MDL of this previous system. After the feasibility studies confirmed the measurement of Mn, the main effort was to improve the MDL values further so as to permit measurements of (i) subjects with low exposure and (ii) non-exposed individuals as well. The aim of this study was to explore the factors required to improve the MDL for the *in vivo* set-up at McMaster University. The main variables of accelerator-based IVNAA are the energy of the projectile and it's current, the irradiation time, counting strategy and concentration of elements in tissue equivalent hand bone phantoms, irradiation cavity and counting system. For this study, all the possible parameters were explored and their effects were studied. Also, this study was done using on an upgraded (in-house) pulse processing system [21]. This article presents the resulting improved calibration curves and MDL with a comparison to previous studies aimed at making the technique useful for low or non-exposed subjects.

Materials and methods

Tissue equivalent hand-bone phantoms containing a solution of Mg, Ca, Na, Cl and Mn in dil. HNO_3 were prepared in 250 ml low density polyethylene (LDPE) Nalgene bottles. The mass of Mn in the phantoms varied from 0.0 to 12.4 mg while the masses of Ca, Na and Cl were kept the same as the phantoms used in earlier measurements [19], based on the data available in ICRP 23 [22]. The mass of Mg was 500 mg in each phantom based on estimations made from recent Mg measurements conducted as part of a study in our Alzheimer's disease patients [23]. Table 1 lists the details of the element masses used with their respective reaction, half-life and their thermal neutron capture cross-section.

As mentioned earlier for this *in vivo* study, an accelerator-based neutron source was used followed by delayed neutron activation analysis. The hand bone phantoms were irradiated in the accelerator beam following one of two protocols of different proton energy, current and irradiation time, *i.e.* (i) 2.0 MeV, 300 μA, 3 min and (ii) 2.3 MeV, 400 μA, 45 s. To measure the gamma activity in the phantoms, a system of eight 10.2 cm × 10.2 cm × 40.6 cm and one 10.2 cm × 10.2 cm × 10.2 cm NaI detectors, arranged in an array of 4π geometry, was used [24]. The irradiated phantoms were then placed inside the gamma counting cavity and the γ-ray spectra from the activated phantoms were acquired. The counting strategy for each phantom was chosen in such a way as to get the contribution of both short- and long-lived isotopes of interest. Average cooling time between the end of irradiation and the start of the count was about 30 s. Counting was done in variable time cycles; for the first 1.5 h the counting was done in 10 min cycles to account for Ca ($T_{1/2} = 8.7$ min) and Mg ($T_{1/2} = 9.46$ min) and after 1.5 h the counting was continued with 30 min cycles for 5–7 h. A typical gamma spectrum acquired for the 12.4 mg of Mn phantom at three different time intervals after the irradiation is shown in Fig. 1, where the strong gamma peaks with their respective elements are also labeled. Detailed neutron dosimetry of the irradiation cavity was also carried out in a separate study using a tissue-equivalent