^1H MRS phantom studies of BNCT ^{10}B -carrier, BPA–F using STEAM and PRESS MRS sequences: Detection limit and quantification

M. Timonen ^{a,b}, A. Kangasmäki ^{a,c}, S. Savolainen ^{a,b,c} and S. Heikkinen ^{a,d,*}

^a *Department of Radiology, Helsinki University Central Hospital, P.O. Box 340, FIN-00029 HUS, Helsinki, Finland*

^b *Department Physical Sciences, University of Helsinki, P.O. Box 64, FIN-00014, Helsinki, Finland*

^c *Department of Laboratory Diagnostics, Helsinki University Central Hospital, P.O. Box 580, FIN-00029 HUS, Helsinki, Finland*

^d *Advanced Magnetic Imaging Centre, Helsinki University of Technology, FIN-02015 HUT, Espoo, Finland*

Abstract. The quantification of boron neutron capture therapy (BNCT) ^{10}B -carrier, L-p-boronophenylalanine-fructose complex (BPA–F) was studied with phantoms using ^1H magnetic resonance spectroscopy sequences PRESS and STEAM at 1.5 and 3.0 T. The results show that typical attainable short echo times of clinical MRS sequences combined with long repetition time result in clinically acceptable quantification accuracy. However, the concentration ratios, which are essential for the treatment planning, can still be reliably measured by using small repetition times. Detection limits of BPA in aqueous phantoms at 1.5 and 3.0 T were evaluated using clinically acceptable measurement time of ~ 10 min, two typical voxel sizes (15^3 and 20^3 mm^3) and PRESS and STEAM sequences. The detection limits of BPA in phantom conditions were 0.7 (3.0 T) and 1.4 mM (1.5 T) for PRESS sequence with 20^3 mm^3 voxel.

1. Introduction

Boron neutron capture therapy (BNCT) is an emerging radiotherapy that is mainly used to treat malignant brain tumors. In the Finnish BNCT trial L-p-boronophenylalanine–fructose complex (BPA–F) is used as ^{10}B -carrier [8]. As the therapeutic dose mainly depend on the tissue ^{10}B concentrations, methods enabling direct *in vivo* concentration measurement are desirable. It has been shown that quantification of BPA is possible using ^1H magnetic resonance spectroscopy (^1H MRS) [5,6,12].

The present study expands our previous phantom study, where ^1H MRS quantification of BPA was presented [6]. In the current study we determined the detection limit of BPA in optimal conditions (aqueous phantom) within clinically reasonable time (~ 10 min) using two typical voxel sizes (15^3 and

*Corresponding author: Sami Heikkinen, Department of Radiology, Helsinki University Central Hospital, P.O. Box 340, FIN-00029 HUS, Helsinki, Finland. Tel.: +358 50 427 1450; Fax: +358 9 471 71342; E-mail: Sami.Heikkinen@hus.fi.

20^3 mm^3) and clinically available STEAM [2] and PRESS [1,3] sequences. This information is essential when judging possibilities to study *in vivo* BPA concentration with ^1H MRS in such situations where BPA concentration is significantly decreased from the peak value, e.g., after neutron irradiation. It has been estimated that tumor and healthy tissue BPA concentrations during the BNCT irradiation are 5–6 and 1–2 mM, respectively [8,10,11]. Furthermore, quantification was performed for more dilute BPA-solutions (2.9 mM and 5.8 mM) compared to the previous study, where the studied BPA concentrations (7.2 mM and 11.5 mM) represented the estimated maximum BPA concentration in patient's brain during BNCT treatment (directly after the infusion of the BPA-F). T_2 -measurements and quantification were performed using both PRESS and STEAM sequences. For this purpose, the response of the BPA's aromatic proton spin system to STEAM sequence with various echo times was determined using simulations. This was done utilizing the similar approach as described earlier for PRESS [6]. Finally, two single voxel spectra were measured from phantom with two vials filled with BPA-solutions of different concentrations. This test was performed in order to investigate whether it would be possible to reliably determine the concentration ratio *in vivo* between the two tissue locations as well as to determine absolute BPA concentrations within a reasonable study time.

In summary, in this study we wanted to determine the detection limit of BPA in phantom conditions and use this result to evaluate the limit *in vivo*. In addition, clinical applicability of usual MRS sequences in quantitative and concentration ratio measurements was tested with phantoms.

2. Materials and methods

2.1. Phantoms

Aqueous solutions with different BPA-concentrations (0.5, 0.7, 1.1, 1.4, 1.8, 2.2, 2.5, 2.9, 5.8 and 23.1 mM) were prepared by diluting similar BPA-F solution as used in the actual treatments (BPA concentration of 144.2 mM). The solutions were transferred into 50 ml round-bottomed flasks. For ^1H MRS measurement the round-bottomed flask was placed in a spherical 4500 ml plastic phantom filled with 0.1 mM MnCl_2 -solution doped with NaCl (0.4%) in order to increase the coil loading to the level typically encountered in human studies.

In the measurements with two-vial-phantom (see Section 2.6) two glass test tubes (OD 32 mm) with BPA concentrations 2.9 and 5.8 mM were placed in a cylindrical plastic phantom filled with NaCl-doped MnCl_2 -solution.

2.2. Experimental details

Clinical 1.5 T and 3.0 T whole body imagers (GE Signa Horizon LX EchoSpeed, GE Medical Systems, Milwaukee, WI, USA) equipped with standard GE transmit/receive head coils were used. ^1H single voxel MR spectra were measured using STEAM and PRESS sequences with CHESS water suppression scheme [4]. In the PRESS sequence, 167° refocusing pulses were used instead of common 180° pulses in order to achieve increased excitation bandwidth. The spectral widths were 2500 Hz (1.5 T) and 5000 Hz (3.0 T) and the number of acquired complex points was 2048. All the spectra were processed and analyzed using SAGE-software (GE Medical Systems, Fremont, CA, USA).

2.3. Simulations

The Virtual NMR Spectrometer simulation program [9] was used to calculate the response of aromatic proton spin system of BPA to the STEAM sequence. The utilized approach was similar to the one described recently for PRESS sequence [6]. Simulations were performed at 1.5 and 3.0 T using echo times (TE) of 20, 35, 50, 75, 95, 125, 150, 250 and 300 ms. Mixing time (TM) was set to 13.7 ms. The measured (see Section 2.4 for experimental details) and simulated STEAM spectra of the aromatic protons of BPA shown in the Fig. 1 do not reveal significant discrepancies suggesting the validity of the simulations.

2.4. T_2 -measurements

T_2 -determinations were performed using aqueous BPA-F phantom (23.1 mM BPA). 1.5 and 3.0 T spectra were recorded using TE-values of 20 (only STEAM), 35, 50, 75, 95, 125, 150, 250 and 300 ms. Measurements were done with 128 scans (16 scans for unsuppressed spectra) using PRESS and STEAM (TM 13.7 ms) sequences. Repetition time (TR) of 1500 ms and voxel size of 20^3 mm^3 was used. All measurements were performed twice. Gaussian apodization with Gaussian line-broadening factor (GB) of 2.0 Hz and one-fold zero filling were performed prior to Fourier transformation. The total intensity of the aromatic proton signals was determined by integrating the chemical shift range 6.7–7.8 ppm.

For PRESS sequence, a ‘collective’ T_2 of the aromatic protons can be determined by fitting the function presented in Eq. (1) with the measured intensities.

$$M_{\text{TE}} = M_{J\text{-evol(TE)}} [M_0 \exp(-\text{TE}/T_2)]. \quad (1)$$

Term $M_{J\text{-evol(TE)}}$ in Eq. (1) describes the calculated intensity at a certain TE obtained from the simulations. For detailed description of the method see [6]. The function used for STEAM sequence is presented in Eq. (2).

$$M_{\text{TE}} = M_{J\text{-evol(TE)}} M_0 \exp(-\text{TE}/T_2) (1 - \exp[(-\text{TR} + \text{TM} + \text{TE}/2)/T_1]) \exp(-\text{TM}/T_1). \quad (2)$$

Water T_2 was determined using Eqs (1) and (2) by omitting the term $M_{J\text{-evol(TE)}}$. The intensities of unsuppressed water signals were determined by Gaussian lineshape fitting. The T_1 -values for water and aromatic protons were obtained from [6].

2.5. Quantification

1.5 and 3.0 T spectra from aqueous BPA-F solution (5.8 and 23.1 mM BPA) were acquired with 128 scans (16 scans for unsuppressed spectra) using voxel size of 20^3 mm^3 and TR of 6000 ms. In addition, a 3.0 T spectrum was recorded also from 23.1 mM phantom. All the measurements were done using both STEAM (TE 20 ms, TM 13.7 ms) and PRESS (TE 35 ms).

Prior to Fourier transformation, exponential apodization (LB 2.0 Hz) and one fold zero filling were applied for 1.5 T data. Intensities of water and aromatic proton signals of BPA were determined using Lorentzian lineshape fitting.

3.0 T data were processed using Gaussian apodization (GB 15 Hz) and one fold zero-filling prior to Fourier transformation. Gaussian lineshape fitting was used to determine intensities of water and BPA.

Fig. 1. Measured and simulated (right) 1.5 T ^1H MR spectra of BPA using STEAM sequence. Chemical shift region 6.7–7.8 ppm is shown. The spectra were recorded from aqueous phantom using 128 scans, TR of 1500 ms and TE values 20, 35, 50, 75, 95, 125, 150, and 300 ms.

Fig. 2. 1.5 T ^1H MR spectra of BPA-F aqueous solutions. BPA concentrations were 2.9 and 5.8 mM. PRESS (128 scans, TE 35 ms, TR 1500 ms) sequence and voxel size 15^3 mm^3 was used. BPA-F aqueous solutions in two test tubes were placed in a cylindrical plastic phantom filled with NaCl-doped MnCl_2 -solution. Positioning of voxels on the T_1 weighted gradient-echo MR image are presented by rectangles.

Heavy apodization was used in order to merge the additional small peaks clearly visible in 3.0 T spectra (Fig. 3b in [6]) into main peaks to facilitate the total intensity determination.

The BPA concentrations were determined using unsuppressed water signal (55.56 M) as an internal concentration reference. Intensities of aromatic proton signal of BPA and water were corrected both for relaxation effects using T_1 -values taken from [6] and T_2 -values presented in this work. T_2 -values determined with STEAM sequence were used in quantification (see Results and discussion). Spectra measured with PRESS sequence were quantified also using T_2 -values determined with PRESS. BPA signals were also corrected for J -evolution effects according to the simulation data. For comparison, concentrations were also determined without any intensity corrections.

2.6. Phantom with two BPA-F vials

1.5 T spectra were recorded from two aqueous BPA-F solutions (2.9 and 5.8 mM BPA). Phantom setup is shown in Fig. 2. Measurements were done using PRESS sequence (TE 35 ms, TR 1500 ms and number of scans 128). Voxel size was set to 15^3 mm^3 . Exponential apodization with LB of 2.0 Hz and one-fold zero filling were used prior to Fourier transformation. Intensity of BPA aromatic signals was measured by integration (6.7–7.8 ppm), whereas unsuppressed water signal intensity was determined by Lorentzian lineshape fitting. Intensity corrections for quantification were performed described in previous section.

2.7. Determination of detection limit

Detection limits of BPA were determined for two voxel sizes (15^3 and 20^3 mm^3) at 1.5 and 3.0 T using both STEAM and PRESS sequences. Spectra were acquired from 0.5, 0.7, 1.1, 1.4, 1.8, 2.2 and 2.5 mM phantoms using 304 scans and TR of 1500 ms, the total duration of a single measurement being ~ 10 minutes (clinically acceptable total duration, includes shimming and water suppression adjustments). TE-values were 35 and 20 ms for PRESS and STEAM, respectively. The TR of 1500 ms was selected as

this is commonly used TR in clinical studies. Furthermore, according to T_1 -value of aromatic protons, it is close to the optimal TR ($\sim 1.3 \cdot T_1$). Data processing was similar as for T_2 -measurements. Signal-to-noise ratio (SNR) for aromatic signals was calculated dividing the amplitude of the signal at 7.3 ppm by 2SD (standard deviation) of the noise calculated from the region 8–10 ppm.

3. Results and discussion

3.1. T_2 -determination

Table 1 shows determined T_2 -values (mean values from the two measurements) for water and BPA. On average, T_2 -values obtained with PRESS are congruent with previous study [6]. Unexpected result is that the T_2 -values determined using STEAM were consistently larger than those obtained using PRESS. This is most likely due to the fact that the TR of 1500 ms is too short with respect to T_1 . This was confirmed by measuring T_2 of water at 1.5 T using PRESS and STEAM sequences and TR of 1500 ms at 1.5 T from gadolinium-diethylenetriamine pentaacetic acid-doped brain metabolite phantom (GE Medical Systems, Milwaukee, WI, USA) with short water T_1 of 650 ms. The obtained water T_2 -values were essentially similar, 310 and 330 ms for PRESS and STEAM, respectively. Furthermore, water T_2 -values at 1.5 T measured from BPA phantom with TR of 1500 ms resulted in 1060 ms (PRESS) and 1900 ms (STEAM). When TR was increased to 6000 ms, the difference between the measured T_2 -values decrease significantly (1700 ms for PRESS and 1800–1900 ms for STEAM). The observed behavior for PRESS can be, at least in part realized by using the intensity equation presented for two-spin-echo imaging including the terms describing T_1 -decay during fractions of TE [7]. This and experimental results clearly suggest that for T_2 -determination, STEAM sequence is more tolerant to the selection of repetition time. Therefore, for the phantom measurements presented in this study we chose to use T_2 -values obtained with STEAM. In addition, as the effects of J -evolution for coupled aromatic spin system of BPA are smaller using STEAM, the accuracy of T_2 -determination probably improves.

The observed discrepancy between the T_2 -values obtained with PRESS and STEAM was significant for aqueous phantoms. Although the T_1 -values *in vivo* are smaller, we suggest that the aforementioned effect should be considered when choosing TR-value for *in vivo* T_2 -measurements. Especially, this TR-dependence should be taken into account when external concentration references are used. This is noteworthy when spectra recorded using longer TE-values are utilized for quantification (the effect of T_2

Table 1
 T_2 relaxation times (ms) of aromatic protons of BPA and water at 1.5 and 3.0 T. T_2 s determined using both STEAM and PRESS sequences are shown

	T_2 (ms)	
	PRESS	STEAM
1.5 T		
BPA	380	510
H ₂ O	1060 (1700, TR = 6000)	1900 (1800–1900*, TR = 6000)
3.0 T		
BPA	250	390
H ₂ O	770	1290

*Determined by manual fitting.

Table 2

Quantification results of BPA-F aqueous phantoms at 1.5 and 3.0 T. The actual BPA concentration is shown in column ‘True’. Results with and without intensity corrections (relaxation and *J*-evolution effects) are presented (columns ‘Corrected’ and ‘Uncorrected’). *T*₂ values of water and BPA determined with STEAM sequence were used for intensity corrections. The quantification results of PRESS spectra obtained using *T*₂ values measured with PRESS are also shown (values in brackets)

Sequence	True <i>c</i> _{BPA} (mM)	Measured <i>c</i> _{BPA} (mM)			
		1.5 T		3.0 T	
		Corrected	Uncorrected	Corrected	Uncorrected
PRESS	5.8	6.3 (6.3)	6.5	5.9 (6.0)	4.8
STEAM	5.8	5.6	5.1	6.4	6.6
PRESS	23.1	–	–	24.8 (25.6)	20.4
STEAM	23.1	–	–	23.2	23.8
PRESS (two-vial phantom)	5.8	6.0 (6.1)	10.0	–	–
PRESS (two-vial phantom)	2.9	3.1 (3.1)	5.1	–	–

differences increases). In such situations *T*₂ of the concentration reference should be measured using sufficiently long TR. Another possibility is to use shorter TR and STEAM sequence.

3.2. Quantification

Quantification results are shown in the Table 2. BPA concentrations determined with and without intensity corrections (*T*₁, *T*₂ and *J*-evolution effects) are presented. The average accuracy ($\pm 7\%$ with and $\pm 12\%$ without intensity corrections) is reasonable using either method but, as expected, the reliability increases when delicate intensity corrections are performed. However, the accuracy of the results obtained without any intensity corrections using typical short TE-values attainable in clinical MRS sequences (special ultra-short-TE sequences are not needed) and long TR-value (6000 ms, typical in quantitative *in vivo* ¹H MRS studies) appears to be sufficient for clinical purposes, especially when the patient cannot tolerate lengthy relaxation time measurements or the available MR-scanner time is limited. It should be also noted that for *in vivo* cases, the relaxation time measurements are hampered by natural temporal decrease of BPA concentration, and therefore careful experiment planning is needed in order to measure *T*₂-values of BPA.

The results obtained using TR of 1500 ms (Table 2, two-vial phantom) clearly point out the necessity for intensity corrections if absolute concentration are needed. However, as expected, the intensity ratio of the measured BPA signals (1.96 : 1) is very close to ratio of real BPA concentrations (2 : 1). In fact, this ability reliably determine the concentration ratio using short TR is essential when *in vivo* boron spatial distribution is studied for treatment planning purpose. The short TR can be either used to decrease the study duration or to increase the SNR by increasing the number of scans. However, it should be noted that low concentration of BPA in healthy brain tissue during BNCT (<2 mM, [8,10,11]) may limit the applicability of concentration ratio determination (see next section).

As was discussed in Section 3.1, *T*₂-values measured with STEAM were chosen for use in intensity corrections. For comparison, the quantification results obtained using *T*₂-values measured with PRESS are also shown in Table 2 (values in brackets). This comparison shows that slight improvement can be achieved, but one should also notice that defects of PRESS are possibly smaller *in vivo*.

3.3. Detection limits

The obtained detection limits for BPA at 1.5 and 3.0 T are shown in Table 3. Figures 3 and 4 present 1.5 and 3.0 T PRESS spectra from 20³ mm³ voxel used in determination of detection limits. Detection

Fig. 3. 1.5 T ^1H MR spectra of BPA-F aqueous solutions (BPA concentrations 1.1, 1.4, 1.8, 2.2, 2.5, 2.9 and 5.8 mM) using PRESS sequence (304 scans, TE 35 ms, TR 1500 ms) and voxel size of 20^3 mm^3 . Expansion from spectral region 5.0–10.0 ppm is shown. Presented signal-to-noise ratios (SNR) for aromatic signals were calculated dividing the amplitude of the signal at 7.3 ppm by 2SD of the noise from the region 8–10 ppm.

Fig. 4. 3.0 T ^1H MR spectra of BPA-F aqueous solutions (BPA concentrations 0.5, 0.7, 1.1, 1.4, 1.8, 2.5 and 5.8 mM) using PRESS sequence (304 scans, TE 35 ms, TR 1500 ms) and voxel size of 20^3 mm^3 . Expansion from spectral region 5.0–10.0 ppm is shown. Presented signal-to-noise ratios (SNR) for aromatic signals were calculated dividing the amplitude of the signal at 7.3 ppm by 2SD of the noise from the region 8–10 ppm.

Table 3

The obtained detection limits for BPA at 1.5 and 3.0 T. Detection limits determined using both PRESS (304 scans, TE 35 ms, TR 1500 ms) and STEAM (304 scans, TE 20 ms, TM 13.7 ms, TR 1500 ms) sequence and voxel sizes of 15³ mm³ and 20³ mm³ are shown

Sequence	Voxel size (mm ³)	Detection limit (mM)	
		1.5 T	3.0 T
PRESS	20 × 20 × 20	1.4	0.7
PRESS	15 × 15 × 15	2.2	1.4
STEAM	20 × 20 × 20	2.2	1.1
STEAM	15 × 15 × 15	5.8	2.5

limit was evaluated by visual inspection of the spectra (three independent observers) i.e. the criterion for the detection was the identification of the typical peak pattern of BPA's aromatic protons (signal to noise ratio ~3).

The detection limits at 1.5 and 3.0 T with for PRESS and 20³ mm³ voxel shows that in phantom conditions it is possible to detect aromatic signals of BPA from sample with BPA concentration under 1.5 mM or even under 1.0 mM (at 3.0 T). Naturally, these values does not strictly hold in *in vivo* circumstances. However, we believe – based on the results of this study – that it is possible to detect ~2 mM concentration even in *in vivo* conditions. The size and placement of the voxel plays major role in obtaining the lowest possible detection limit (see Table 3). Inhomogenous (containing bone and possible cavities) tissue within the voxel may easily lead to non-optimal magnetic field homogeneity and therefore broadened lines. This combined with small voxel size will result in very low signal-to-noise ratio causing significant inaccuracy to the concentration values measured *in vivo*.

4. Conclusions

According to the presented phantom results, the detection limit of BPA in optimal phantom conditions using measurement time ~10 min was found to be 0.7 and 1.4 mM at 3.0 and 1.5 T, respectively. Therefore, we assume that concentrations of about 2 mM can be detected *in vivo*.

It is possible to measure the BPA concentrations with clinically acceptable accuracy of about ±12% without any delicate intensity corrections, provided that short TE and sufficiently long TR are utilized. If the determination of concentration ratios is sufficient, it is possible use short TR in studying the temporal and spatial concentration distribution.

Based on the promising phantom results of this work we are currently proceeding to actual *in vivo* ¹H MRS studies of BPA approved by the Ethics Committee of the Department of Surgery in Helsinki University Central Hospital.

Acknowledgements

Professor David Fushman is acknowledged for providing us the Virtual NMR Spectrometer simulation program. Head provisor Merja Rasilainen and provisor Jonna Leinonen from the Helsinki University Hospital Pharmacy are acknowledged for preparing the BPA-F. This study has been financially supported by the Finnish Academy and by a research grant of the Department of Radiology from the State Subsidy for Helsinki University Central Hospital.

References

- [1] P.A. Bottomley, Spatial localization in NMR spectroscopy in vivo, *Ann. N.Y. Acad. Sci.* **508** (1987), 333–348.
- [2] J. Frahm, K.-D. Merboldt and W. Hänicke, Localized proton spectroscopy using stimulated echoes, *J. Magn. Reson.* **72** (1987), 502–508.
- [3] R.E. Gordon and R.J. Ordidge, Volume selection for high-resolution NMR studies, in: *Book of Abstracts: Third Annual Meeting of the Society of Magnetic Resonance in Medicine*, SMRM, Berkeley, 1984, p. 272.
- [4] A. Haase, J. Frahm, W. Hänicke and D. Matthaei, ^1H proton NMR chemical shift selective (CHESS) imaging, *Phys. Med. Biol.* **30** (1985), 341–344.
- [5] S. Heikkinen, A. Kangasmäki, L. Kankaanranta, A.-M. Häkkinen, N. Lundbom, J. Vähätalo and S. Savolainen, ^1H MRS studies of the BNCT ^{10}B -carrier, BPA-F. Towards quantification, in: *Research and Development in Neutron Capture Therapy*, W. Sauerwein, R. Moss and A. Wittig, eds, Essen, Germany, September 8–13, 2002, Moduzzi Editore, Bologna, 2002, pp. 949–953.
- [6] S. Heikkinen, A. Kangasmäki, M. Timonen, L. Kankaanranta, A.-M. Häkkinen, N. Lundbom, J. Vähätalo and S. Savolainen, ^1H MRS of a boron neutron capture therapy ^{10}B -carrier, BPA-F: phantom studies at 1.5 and 3.0 T, *Phys. Med. Biol.* **48** (2003), 1027–1039.
- [7] R.E. Hendrick, Image contrast and noise, in: *Magnetic Resonance Imaging*, D.D. Stark and W.G. Bradley, eds, 3rd edn, Mosby Inc., St. Louis, 1999, pp. 52.
- [8] H. Joensuu, L. Kankaanranta, T. Seppälä, I. Auterinen, M. Kallio, M. Kulvik, J. Laakso, J. Vähätalo, M. Kortenesniemi, P. Kotiluoto, T. Seren, J. Karila, A. Brander, E. Järviluoma, P. Ryyänänen, A. Paetau, I. Ruokonen, H. Minn, M. Tenhunen, J. Jääskeläinen, M. Färkkilä and S. Savolainen, Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine, *J. Neuro-Oncol.* **62** (2003), 123–134.
- [9] P. Nicholas, D. Fushman, V. Ruchinsky and D. Cowburn, The virtual NMR spectrometer: a computer program for efficient simulation of NMR experiments involving pulsed field gradients, *J. Magn. Reson.* **145** (2000), 262–275.
- [10] P. Ryyänänen, A. Kangasmäki, P. Hiismäki, J. Coderre, A.Z. Diaz, M. Kallio, J. Laakso, M. Kulvik and S. Savolainen, Non-linear model for the kinetics of ^{10}B in blood after BPA-fructose complex infusion, *Phys. Med. Biol.* **47** (2002), 737–745.
- [11] P. Ryyänänen, M. Kortenesniemi, J.A. Coderre, A.Z. Diaz, P. Hiismäki and S. Savolainen, Models for estimation of the ^{10}B concentration after BPA-fructose complex infusion in patients during epithermal neutron irradiation in BNCT, *Int. J. Radiat. Oncol. Biol. Phys.* **48** (2000), 1145–1154.
- [12] C.S. Zuo, P.V. Prasad, P. Busse, L. Tang and R.G. Zamenhof, Proton nuclear magnetic resonance measurement of p-boronophenylalanine (BPA): A therapeutic agent for boron neutron capture, *Med. Phys.* **26** (1999), 1230–1236.