The Analysis of Trace Multielements in the Prescriptions of Chinese Herbs Using INAA and ENAA

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The elemental concentrations of two Chinese herbal prescriptive medicines were analyzed using Instrumental Neutron Activation Analysis (INAA) and Epithermal Neutron Activation Analysis (ENAA). For the purpose of treating disease and maintaining good health, these herbal medications have been commonly used to strengthen the spleen and recoup the vital energy consumed by Taiwanese children. The concentrations of Al, Cl, Co, Cr, Fe, K, Na Sc, and Zn were determined by INAA, and As, Cd, Mn, and Sb were determined by ENAA. The values of elements analyzed both by INAA and ENAA were in excellent agreement with values reported in published data. The ranges of elemental concentrations were found to vary from 10^4 to 10^{-3} μg/g from one prescription to the other. The maximum daily intakes (MDI) of toxic metals, As, and Cd were within acceptable WHO/RDA limits.

Key words: Chinese herbs, INAA, ENAA

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Introduction

In Chinese traditional herbal medicine, many popular and secret formulas purported to strengthen the spleen, benefit vital energy, regulate the stomach and eliminate the evil of dampness. These problems can be manifested as diarrhea, poor appetite, and the feeling of oppression or heaviness in the chest. There are numerous prescriptions in traditional Chinese medical literature. In fact, crude herbs and secret formulas have been the key source of health-care in Asia and are still commonly depended on today by the population at Taiwan.[1,2] Certifications of trace elemental concentrations in Chinese herbs are still of primary interest to many laboratories in medical science.

The role of Instrumental Neutron Activation Analysis (INAA) in the determination of trace elements has steadily increased in importance mainly because of its high sensitivity and multi-element capability and because the method is free of blank values from reagents if these are added after activation. However, one serious limitation of INAA is that the more abundant matrix elements become strongly activated during irradiation and their intense activities obscure to the lower concentrations of elements. In addition, long counting times are needed in order to obtain good precision. Such long waiting times preclude the detection of radionuclides with half-lives shorter than or comparable to those of interfering activities and generally reduce the analytical usefulness of INAA.

In the elemental analysis of raw herbs, ^{24}Na, ^{38}Cl and ^{82}Br produce the bulk of interfering activities and consequently their half-lives determine the speed of INAA. If short-lived isotopes are utilized and transfer facilities are available, INAA has always been an excellent method of determining these isotopes in a variety of biological matrices with Minimum Detection Concentration (MDC) better than 1 μg/g. However, when trying to measure As and Cd at very low concentrations, INAA may not be the ideal choice.

Epithermal Neutron Activation Analysis (ENAA) is performed by enclosing samples in thermal neutron filters such as cadmium or boron and removing thermal neutrons from reactor neutrons. ENAA has been applied to various sample matrices including geological and biological materials geological samples and biological materials,[3,4] blood,[5,6] infant formula, milk, protein-bond iodine,[7] foods,[8,9] geological sample and biological reference materials.[3,10] In this study, the ENAA technique is compared with the conventional INAA technique in terms of ratio (*R*), advantage factor (*AF*), MDC and the time scales obtained from the analysis of Chinese herbal prescriptions.

Materials and Methods

Sample preparation

Two kinds of prescribed medicines were selected for analysis: Seng-Ling-Bai-Hu-Hsien (SLBHH) and Syh-Jiun-Tzyy-Tang (SJTT), both of which are mixed with various kinds of raw materials comprised of Chinese herbs according to traditional prescriptions developed in China.[1,2] Generally, 118g of SLBHH is prepared by mixing the following ingredients: 15g of Codonopsis Pilosulae, 15g of Dioscoreae, 15g of Dolichoris Album, 15g of Coicis, 20g of Nelumbinis, 10g of Atractylodis Macrocephalae, 10g of Poriae Alba, 6g of Glycyrrhiazae Praeparata, 3g of Amomi, 3 g of Platycodi, and 6g of Ziziphi Jujubae. 35 grams of SJTT contained: 10g of Codonopsis Pilosulae, 10g of Atractylodis Macrocephalae, 10g of Poria and 5g of Glycyrrhizae Praeparata.[1,2] Generally, these herbal ingredients are commonly used for treating young children in Taiwan.

These ingredients, used together to strengthen the spleen and enhance vital energy, regulate the stomach and eliminate the negative effects of dampness, are imported from different regions of China. However, toxic elements such as As and Sb have often unlawfully added and consequently cause clinical diseases due to chronic metallic poisoning. Five samples (1000g each) of each herb, each were taken from various local pharmaceutical shops endorsed by medical doctors. Samples for INAA analysis weighed between 150 and 200 mg and 300-350 mg ENAA analysis. When purchased, all prescriptions were made up dried materials in their original forms. For the neutron activation analysis of these prescriptions, the dried samples were packed into a double-sealed 2×2 cm^2 polyethylene bag in the vertical tube (VT) irradiation positions for long irradiation and pneumatic tube (PT) irradiation positions for short irradiation of the Open Pool Reactor at National Tsing Hua University (THOR) as listed at Table 1. An empty bag of identical type and size was taken for blank correction, while samples were also irradiated with the standards used for the quantitative analysis of elements in samples and cross checking therein. Lichen (IAEA -336) was chosen as the standard for determining elemental concentrations. The analysis was done in the same way as described above. The weights of standards in this work were also about 150mg and 350 mg, respectively. Each sample and standard was prepared in triplet to minimize the statistical uncertainty.[12]

Irradiation filters

The larger boron-polyethylene (BPE) flexible shield cylinder container of *164 mm H × 44 mm D with 3.2 mm* wall thickness and smaller cadmium cylinder container of *40 mm H × 25 mm* D with *1 mm* wall thickness filter were used to screen thermal neutrons as shown at Fig 1 (a,b) in this study. The boron shields were made from a 3.2 mm thick BPE loaded with 30% w/w natural boron (Flex/Boron, Reactor Experiments, UK).[13] BPE cylinders were made to fit into VT irradiation positions for long irradiation.

γ-spectra analyzed

For the neutron activation analysis of Chinese herbs, all irradiations were carried out in the THOR 1 MW reactor in two irradiation positions at the neutron flux of 3.5×10^{12} n $cm^{-2}s^{-1}$ PT and 1×10^{12} n $cm^{-2}s^{-1}$ VT positions using INAA.[14] Epithermal irradiations were performed using polyethylene sealed sleeve packed BPE and Cd containers in VT position. The estimated epithermal neutron flux was 1.4×10^{12} n $cm^{-2}s^{-1}$ in the PT and 1.1×10^{11} n $cm^{-2}s^{-1}$ in the VT for

Table 1 Optimum irradiating (t_i), decay (t_d) and counting (t_c) conditions

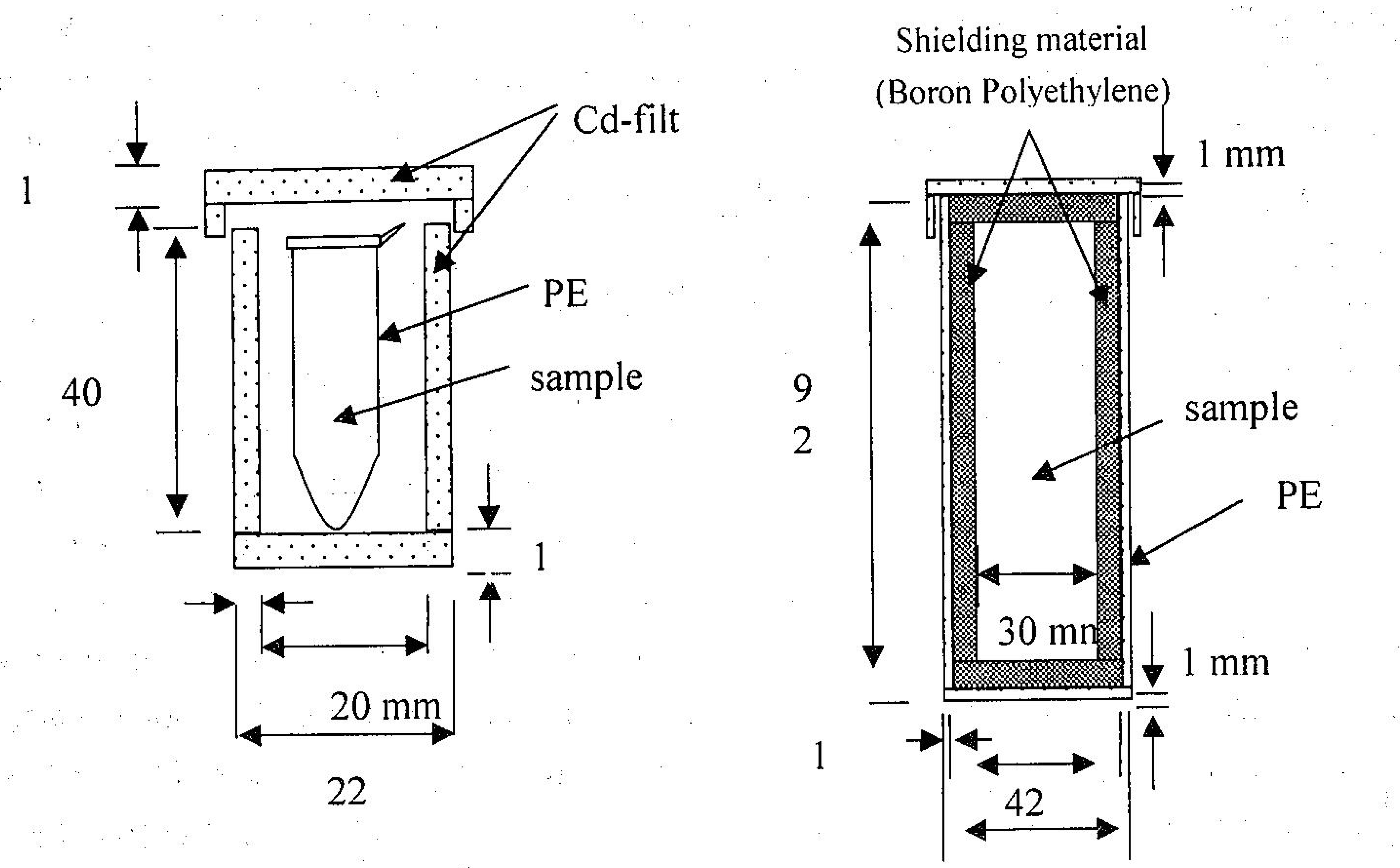
Neutron shield	Irradiation position	Method	Nuclide	t_i	t_d	t_c
None	PT[a]	INAA	^{24}NA, ^{28}Al, ^{38}Cl, ^{42}K,	5 min	2 min	5 min
Cd	PT[b]	ENAA	^{56}Mn	10 min	10 min	5 min
None	VT[c]	INAA	^{46}Sc, ^{51}Cr, ^{59}Fe, ^{60}Co, ^{65}Zn	24 h	30-45 d	20 min
BPE Sheet	VT[d]	ENAA	^{76}As, ^{115}Cd, ^{122}Sb,	24 h	1-2 d	20 min

[a]Neutron flux 3.5×10^{12} n $cm^{-2}s^{-1}$

[b]Epithermal neutron flux 1.4×10^{11} n $cm^{-2}s^{-1}$

[c]Neutron flux 1×10^{12} n $cm^{-2}s^{-1}$

[d]Epithermal neutron flux 1.1×10^{11} n $cm^{-2}s^{-1}$



(a) Cadmium filter container (b) Boron Polyethylene filter container.

Fig. 1 (a) Cadmium filter container; (b) Boron Polyethylene filter container.

ENAA. Irradiation schemes were developed: short irradiations (t_i = 5, 10min) in the PT and long irradiations (t_i = 24 h) in the VT. All of the irradiation procedures are shown in Table 1. The 10 mg Ni metals have been counted to correct for the neutron fluctuation during irradiation and published everywhere.[12,14] The γ-ray spectra were calculated using the calibrated HPGe detector with 15% relative efficiency with 2.5 keV (FWHM) resolution at 1333.2 keV of ^{60}Co. γ-ray spectra were analyzed by Micro SAMPO90 software with personal computer connecting to a System-100 multichannel analyzer (MCA) board for spectral acquisition.[15] Statistical errors in each of these values did not exceed 15% and dead times were kept below 10%. The element contents and MDCs were determined by means of Currie citation at 95% confidence level in experimental conditions.[16] Irradiating, decaying and counting times were optimized after a series of experimental test measurements for all irradiation techniques.

Ratio and advantage factor

To evaluate the usefulness of ENAA relative to INAA for irradiation times of the short and long irradiations, lichen was analyzed. The MDCs of the analysis of lichen by INAA and ENAA varied from 10^{-4} to 140 μg/g. These experimental parameters can be considered reasonable for rapid instrumental determination of radionuclides with half-lives ranging from a few minutes up to several years. For concentrations of As, Cd, and Sb, the container gave the best and lowest MDC. BPE containers were useful in determining As, Cd and Sb levels down to 9, 20 and 5 ng/g, respectively, in this study. The most important requirement for a given element to be determined with high sensitivity by ENAA is the ratio of its resonance integral to thermal neutron cross-section (RI/σ_0). These values are given in Table 2 for the radionuclides used in the analysis. The values for the element contents and the optimum irradiating (t_i), decaying (t_d) and counting (t_c) conditions are listed in Table 1. In a BPE container, these decay times are determined essentially by the level of sample activity that can be measured with the decay period up to 1-2 days. However, the mechanical integrity of these containers was not that great and they started to chip off on repeated use.

Results

The enhancement of a radionuclide is normally expressed as the advantage factor (*AF*), which is the ratio of the cadmium and boron ratios $(R_{Cd}, R_{BPE})_{Na}/(R_{Cd}, R_{BPE})_X$, where $(R_{Cd})_{Na}$, $(R_{BPE})_{Na}$ and $(R_{Cd})_X$, $(R_{BPE})_X$ denote the interfering nuclide (^{24}Na) and the nuclide of interest (X), respectively.[3,4,16,17] The main interfering elements are Na, Cl and Br in Chinese herbs; therefore, we chose Na, activated to ^{24}Na, as the standard interfering isotope. The theoretical and experimental *AF* s have been reported for elements of interest in geological samples, ores, and bloods which show enhancement of many trace elements irradiated under boron and cadmium filters.[3,4] It can be observed that the R_{BPE} are much better than R_{Cd}, because the cut-off energy of boron for neutrons is higher than that of cadmium. The *AF* s of As, Cd, Mn and Sb ranged from 0.027 to 0.3 times higher than those of the interfering nuclides in ENAA as compared to INAA, respectively. *AF* s were in agreement with the reference values as shown in Table 2.[4] Thus, ENAA proved suitable for the analysis of As, Cd, Mn and Sb in Chinese herbs.

Discussion

Cadmium and BPE filter

Cadmium filters have disadvantageous in as far as samples must be encased in polyethylene bags or boxes; furthermore, samples emerging from the reactor are highly radioactive and must be handled in a hot cell for safety reasons. To eliminate this problem, BPE flexible shield cylinder containers have been chosen for the longer durations of irradiation. BPE containers were found to be superior in that a decay of up to 1.5d permits safe handling of the BPE shields, allowing the samples to be counted without further treatment.

The 3.2mm thick BPE shield container was found to be able to conveniently accommodate the samples, blank and standard. Cd was an effective shield for the analysis of elements with a resonance peak energy of (n, γ) reaction lower than 2 eV. The resonance peak energy of the reaction of $^{55}Mn(n, \gamma)\,^{56}Mn$ is 412 eV. Thus, the boron compounds were better than Cd in this particular case. From Table 2, the *R* and *AF* of the elements we studied using BPE container as a shield were slightly lower than those when we used Cd as a shield.

Interference

Arsenic is a volatile element when its temperature exceeds 500℃ and may loss at this temperature.[19] Our results indicate no significant loss during the 24h of irradiation using double-sealed samples at an epithermal neutron flux of 10^{11} $ncm^{-2}s^{-1}$. As the polyethylene bags used for packing may have their own elements, all of the polyethylene bags and containers were soaked in 1:1 HNO_3 for 3 days and washed with deionized water. The empty bags of identical type and size were taken as blank correction and analyzed as mentioned above in the same conditions.

The ENAA procedures were applied to the determination of As, Cd, Mn and Sb in a variety of prescriptions purchased from local pharmaceutical shops in Taiwan. These results are displayed in Table 3. The prime sources of systematic error

Table 2 Ratio (*R*) and Advantage Factor (*AF*) of Cadmium and Boron Polyethylene containers

Element	Nuclear reaction	γ-Ray energy (keV)	RI/σ_0	Cadmium		Boron Polyethylene Sheet	
				R_{Cd}	AF_{Na}	R_{BPE}	AF_{BPE}
Na	$^{23}Na(n,\gamma)^{24}Na$	1368.6	0.57	41.6	0.16	61.2	0.13
Al	$^{27}Al(n,\gamma)^{28}Al$	1779.0	1.05	23.7	0.27	N. A	N. A.
Cl	$^{37}Cl(n,\gamma)^{38}Cl$	1642.7	0.49	47.2	0.14	N. A.	N. A.
Mn	$^{55}Mn(n,\gamma)^{56}Mn$	846.8	1.04	21.5	0.30	N. A.	N. A.
As	$^{75}As(n,\gamma)^{76}As$	559.2	14.65	N. A.	N. A.	6.29	0.041
Br	$^{81}Br(n,\gamma)^{82}Br$	554.4	16.67	N. A.	N. A.	4.84	0.036
Cd	$^{114}Cd(n,\gamma)^{115}Cd$	336.6	10.0	N. A.	N. A.	2.81	0.027
Sb	$^{121}Sb(n,\gamma)^{122}Sb$	564.1	N. A.	N. A.	N. A.	3.63	0.031

[a] Not available

Table 3 Elemental concentrations in prescriptions of SLBHH and SJTT as well as Maximum Daily Intake by Taiwanese Children

Element	SLBHH		SJTT		RDA[b]	PTI[c]
	Concentration	MDI[a]	Concentration	MDI[a]		
K(mg/g)	12.1(21)[d]	18.2	12.8(21)	19.2	-	-
Cl(mg/g)	1.04(12)	1.56	1.42(58)	2.13	-	-
Al(mg/g)	0.82(13)	1.23	1.07(82)	1.61	-	-
					-	-
Na(μg/g)	417 (90)	626	562 (61)	843	-	-
Fe(μg/g)	370 (100)	555	254 (53)	381	15000	-
Mn(μg/g)	63 (24)	95	52 (17)	78	2000	-
Zn(μg/g)	17.5(32)	26	22.5(64)	34	15000	-
Cr(μg/g)	7.3(59)	11	1.04(16)	1.56	50	-
As(μg/g)	0.57(49)	0.86	0.20(14)	0.30	-	30
					-	-
Co(ng/g)	303 (57)	455	341 (44)	511	-	-
Sc(ng/g)	69 (71)	104	59 (27)	89	-	-
Cd(ng/g)	20.7(38)	31	95 (13)	143	-	15000
Sb(ng/g)	14 (10)	21	N. D.[e]	N. D.	-	-

[a] Maximum daily intakes by children with a dose of 1.5 g/day.

[b] US Recommended Dietary Allowances (10th ed.) for adults.

[c] Provisional tolerable intakes (WHO/FAO) for 15 kg body weight children.

[d] Here and elsewhere in this paper, the number in the parentheses indicates the uncertainty of the last digits of the mentioned values, that is 12.1(21)=12.1±0.21.

[e] Not detected in this work.

rose in this table mainly from counting geometries. These were minimized through experimental design by ensuring identical conditions for both standard and samples.

γ -spectra analyzed

In the long irradiations of 24h followed by 1-2d decay, the elements could be determined rapidly with reasonable sensitively by BPE container. The *AF* was utilized to rapidly determine PBE cover. Initial results using INAA proved to be unsuccessful primarily due to the interfering ^{24}Na and ^{82}Br γ -rays, resulting in high backgrounds from these strong peaks.[24] The main peak of As at 559.2 keV is usually made difficult by the strong interference from 554.4 keV ^{82}Br as well as by Compton scattering from 1368.6 keV ^{24}Na as shown a Fig 2. Both isotopes have comparable RI/σ_0 ratios and half-lives. The 554-559 twin peaks were sufficiently resolved in epithermal activation by the SAMPO90 software in this study. After 1.5d decay, the 2.54h 846.8 keV ^{56}Mn could not be measured with BPE cover. 336.2 keV photon, sitting on Compton continuum, cannot be ideally used in BPE covers; hence, the precision of Cd is lower. Landsberger demonstrated that a combined use of ENAA and Compton suppression system optimized the determination of cadmium.[20] In the long irradiations of 24 h, lichen was analyzed after 7 and 30d of irradiation in the THOR facility, respectively. For epithermal activation, the earliest time of the γ -spectra obtained of the samples could be about 3-4 times than a result of the reduction in the ^{24}Na, ^{38}Cl and ^{82}Br background activity. In general, MDCs are obtained with thermal activation particularly for median-lived radionuclides, e. g. ^{56}Mn, ^{76}As, ^{122}Sb and ^{115}Cd. For the measurement of As, ENAA is a preferred method as its RI/σ_0 value is high, also because its half-life is comparable to that of ^{24}Na. However, ENAA, with long waiting times up to 10d, is undesirable. One of the basic findings of this study was that As, Cd, Mn and Sb can be found rapidly with reasonable sensitivity by ENAA.

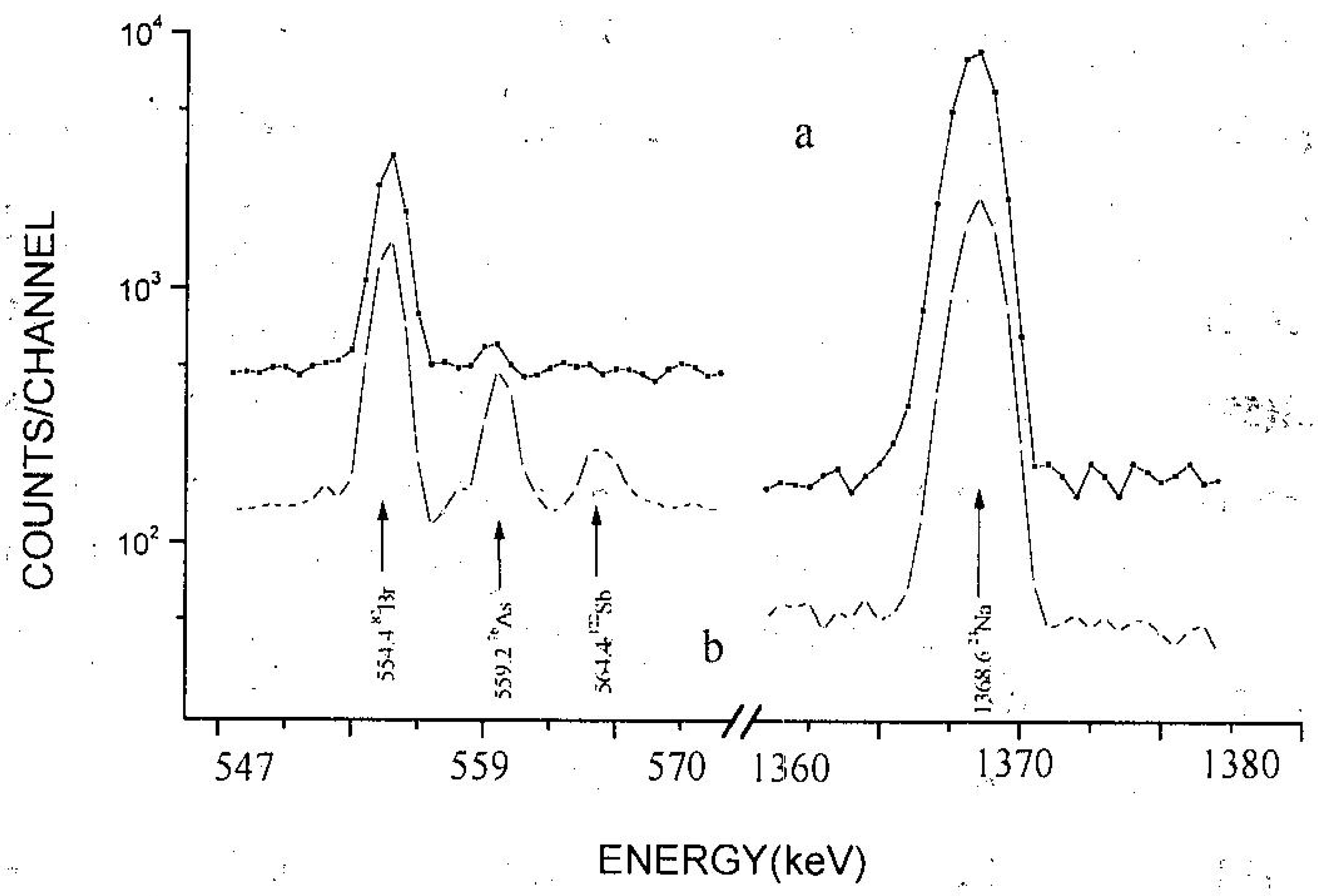


Fig. 2 Gamma-ray spectra for Seng-Ling-Bai-Hu-Hsien (SLBHH) (a) without and (b) with BPE filter container for long time irradiation. Sample volume (a) 160 mg and (b) 450 mg, irradiation time (a) 24 hour and (b) 24 hour, cooling time (a) 1.5 days and (b) 5 days, counting time (a) 20 min and (b) 20 min.

Assessment of elements of Chinese prescriptions on health effects

The existence of 13 trace elements, Al, As, Cd, Cl, Co, Cr, Fe, K, Mn, Na, Sb, Sc, and Zn in the investigated Chinese herbs indicates their value and importance to the Taiwanese. Elemental concentrations of these prescriptions are in excellent agreement with values reported in published data elsewhere.[21-24] It is interesting to estimate the maximum daily intakes (MDI) of these trace elements in these prescriptions. Table 3 summarizes the measured average intake for 13 selected elements per day and person, based on the fact that the average body weight of a 3-year-old child is 15kg. In our analysis of SLBHH, a popular Chinese medicine for young children, Fe can be observed to have an MDI 555 μg/g lower than the values of US Recommended Dietary Allowances. As and Sb are inherently toxic and may be originate from cultivation farm environment or imported from China. The MDI of As is 0.86 μg/g in SLBHH and 0.30 μg/g in SJTT as shown in Table 3. These values are also lower than the US Recommended Dietary Allowances (10th ed.) for adults.[25] Even if a child takes the maximum dose, s/he would ingestion daily 0.86 μg/g of As, 31 ng/g Cd measured by SLBHH and 0.30 μg/g of As and 143 ng/g Cd measured SJTT, amounts that still fall within the provisional tolerable intakes (WHO/FAO) for 15 kg body weight children recommend by FAO/WHO.[25] The carcinogenic effects of inorganic arsenic compounds in human beings are well known. In other words, it is quite safe to consume these prescriptions. In fact, all trace elements may be toxic if consumed in large enough quantities for long enough periods of time. Such data may be useful in assessing the accumulation of toxic elements and their effects on the human organism.

Conclusion

For the proposes of strengthening the spleen and improving vital energy, regulating the stomach and eliminating the negative effects of dampness, two prescriptions of Chinese herbs, Seng-Ling-Bai-Hu-Hsien (SLBHH) and Syh-Jiun-Tzyy-Tang (SJTT) are frequently consumed by Taiwanese children. The concentrations of Al, As, Cd, Cl, Co, Cr, Fe, K, Mn, Na, Sb, Sc, and Zn trace elements have been found to range from 10^4 to 10^{-3} μg/g in these herbal prescriptions. The reliability of the determinations achieved by ENAA using BPE and Cd filter is comparable with that of INAA, so the MDCs of elements that can be evaluated. ENAA may be more advantageous than INAA in that it reduces interfering activity by about 3 - 4 times. It can be utilized for the rapid determination of As, Cd, Mn and Sb trace elements in the prescriptions we studied accurately and reliably. Although the medications contain the toxic elements, As and Cd, it is still quite safe for Taiwanese children to consume these two medicines.

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