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Monitoring of mercury, arsenic and lead in traditional Asian herbal preparations on the Dutch market and estimation of associated risks

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Keywords: Ayurveda; Traditional Chinese Medicine; Traditional Tibetan Medicine; herbal remedies; dietary supplements; heavy metals; bhasmas; mercury; arsenic; lead

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Abstract

Traditional herbal preparations (THPs) used in Ayurveda, Traditional Chinese Medicine (TCM), Traditional Tibetan Medicine (TTM) and other Asian traditional medicine systems may contain significant amounts of mercury, arsenic or lead. Though deliberately incorporated in Asian THPs for therapeutic purposes, these constituents have caused intoxications worldwide. The aim of this study was therefore to determine mercury, arsenic and lead levels in Asian THPs on the Dutch market. 292 THPs used in Ayurveda, TCM and TTM were sampled between 2004 and 2007. Samples were mostly multi ingredient THPs containing herbs and minerals. The labeling of less than 20% of the THPs suggested the presence of mercury, arsenic or lead. These elements were shown by ICP-MS in 186 (64%) of 292 THPs. Estimated weekly mercury, arsenic and lead intake levels were calculated for each THP from the analytically determined concentrations and the recommended dose. 59 THPs (20%) were likely to result in intakes of these elements significantly exceeding safety limits. Of these 59 THPs, intake estimates for 50 THPs significantly exceeded the safety limit for mercury (range 1.4 - 1747 mg/wk); intake estimates for 26 THPs significantly exceeded the safety limit for arsenic (range 0.53 - 427 mg/wk) and intake estimates for 8 THPs were significantly above the safety limit for lead (range 2.6 - 192 mg/wk). It is concluded that the mercury, arsenic and lead contents of THPs used in Ayurveda, TCM and TTM remain a cause for concern and require strict control.

Running title: Hg, As & Pb in Asian herbal preparations

Keywords: Ayurveda; Traditional Chinese Medicine; Traditional Tibetan Medicine; herbal remedies; dietary supplements; heavy metals; bhasmas; mercury; arsenic; lead

Introduction

In Asian traditional medicine systems such as Traditional Chinese Medicine (TCM), Traditional Tibetan Medicine (TTM) and the Indian traditional medicine systems Ayurveda, Unani-Tibb and Siddha, traditional herbal preparations (THPs) play an important role (Bajaj & Vohora, 2000; Aziz et al., 2002; Patwardhan et al., 2005; Sallon et al., 2006). In the Netherlands Asian THPs can be brought on the market as food supplements, which do not require prior safety evaluation. Asian THPs have been reported to contain herbal toxic principles, undeclared synthetic drugs and significant amounts of mercury, arsenic and lead (Espinoza et al., 1995; Johanns, 2002; Ernst, 2002b; Blok-Tip et al., 2004; Saper et al., 2004; Mino & Yamada, 2005; MHRA, 2005; Rietjens et al., 2005; Martena et al., 2006; Martena et al., 2007). Use of Indian, Tibetan and Chinese THPs has resulted in lead poisonings worldwide and several mercury and arsenic intoxications as well (Dunbabin et al., 1992; Kang-Yum & Oransky, 1992; Kew et al., 1993; Thatte et al., 1993; Keen et al., 1994; Prpic-Majic et al., 1996; Wu et al., 1996; Li et al., 2000; Moore & Adler, 2000; van Vonderen et al., 2000; Auyeung et al., 2002; Tait et al., 2002; CDC, 2004; Lee et al., 2004; Schilling et al., 2004; Khandpur et al., 2008). In Ayurveda, Siddha, Unani-Tibb, TTM and TCM ingredients high in the metals mercury and lead or the metalloid arsenic are added to THPs for therapeutic purposes (Kang-Yum & Oransky, 1992; Thatte et al., 1993; Bajaj & Vohora, 2000; Aziz et al., 2002; Sallon et al., 2006). In TCM tranquilizing and detoxifying effects are attributed to mercury (Kang-Yum & Oransky, 1992) and nearly 10% of the formulas in the Pharmacopoeia of China incorporate the mercury containing mineral cinnabar (Young et al., 2002; Huang, 2006). In 25% of the 634 formulas for Ayurvedic THPs in the official Ayurvedic Formulary of India, mercury, lead and arsenic compounds are listed as ingredients (Ministry of Health, 2000; Ministry of Health, 2003). An Ayurvedic discipline called ‘Rasa shastra’ is dedicated to the study of the therapeutic use of mercury and other metals or metalloids (Dash et al, 1986). In most cases high levels of metals or metalloids in Ayurvedic THPs result from intentional incorporation of certain metallic preparations called ‘bhasmas’ in the products. The metals and metalloids in bhasmas are claimed to be detoxified by elaborate processing steps including many cycles of heating and subsequent cooling in herbal mixtures and animal products such as cow’s urine or ghee (Thatte et al.,

1993; Ravinarayan & Skandhan, 1995; Ministry of Health, 2000; Ministry of Health, 2003; Kumar et al., 2006). Comparable preparations called kushtas and parpams are in use in Unani-Tibb and Siddha, respectively (Bajaj & Vohora, 2000; Aziz et al., 2002).

Metals and metalloids can exist in different defined chemical species and the toxicity of these species can vary significantly (WHO, 2006). Available reports consistently point to the presence of inorganic metal or metalloid compounds in Chinese, Tibetan and Indian THPs including Ayurvedic THPs. Naga bhasma, a widely used Ayurvedic lead preparation (Ministry of Health, 2000), contains lead sulfide (PbS); other lead preparations contain lead oxide (PbO) or lead sulfate (PbSO₄) (Ravinarayan & Skandhan, 1995; Kumar et al., 2006). In TCM, lithargyrum or 'mi tuo seng' (PbO) is used (Bensky & Barolet, 1990). Important Ayurvedic mercury preparations are 'parada' (purified mercury), 'hingula' (cinnabar, HgS), 'kajjali' (HgS) and 'makaradhvaja' (HgS) (Kumar et al., 2006; Himalaya, 2008). In TTM processed mercury preparations (tsothel) are used as well, which mainly consist of mercuric sulfide (HgS) and smaller amounts of mercuric sulfite (HgSO₃) and mercuric sulfate (HgSO₄) (Sallon et al., 2006). In TCM mercury is used as cinnabar (zu sha) and as calomel (qing fen, Hg₂Cl₂) (Bensky & Barolet, 1990; Kang-Yum & Oransky, 1992; Bensky & Gamble, 1993; Mino & Yamada, 2005; Cooper et al., 2007). In both Chinese and Ayurvedic THPs, realgar (As₄S₄), orpiment (As₂S₃) and arsenolite (As₂O₃) are used but in Ayurveda these minerals are processed before use (Bensky & Barolet, 1990; Bensky & Gamble, 1993; Mino & Yamada, 2005; Cooper et al., 2007; Liu et al., 2008b). In certain kushtas (used in Unani-Tibb) As₂O₃ was found but kushtas can contain other inorganic arsenicals as well (Aslam et al., 1979; Kew et al., 1993; Aziz et al., 2002).

In 2004 the Dutch Food and Consumer Product Safety Authority (VWA) received reports of two cases of lead poisoning linked to the use of Ayurvedic THPs from, respectively, India and Nepal (VWA, 2005; Kanen & Perenboom, 2005). These cases prompted the VWA to intensify investigations into metal and metalloid contents of Asian THPs. The objective of this investigation was to study the metal and metalloid contents of Asian THPs on the Dutch market and assess the related risks by comparing the estimated metal and metalloid intake resulting from use at the proposed dose levels to established toxicological safety limits. The current report presents the results of this study.

Material and methods

Sampling

VWA inspectors sampled 292 Asian THPs for oral use on the Dutch market between December 2004 and June 2007. The aim of the sampling plan was to collect commercially available Asian THPs that could potentially contain significant amounts of mercury, arsenic or lead. Samples were of Ayurvedic, Chinese and Tibetan origin and were directly collected from importers, producers and vendors throughout the Netherlands. The locations were selected from the VWA inspection database or identified by an internet search. No THPs were purchased via Internet. Per product, one or more units of at least 20 g were sampled. Criteria for inclusion were an apparent relation to Ayurveda, TCM or other traditional Asian medicine systems and the presence of ingredients used traditionally in these medicine systems. THPs lacking such features were excluded. For instance, a food supplement made in China with the contemporary ingredient spirulina or an American supplement with the traditional ingredient gingseng but lacking a link with TCM, would be excluded. Sampling was aimed at multi ingredient THPs with herbs and minerals but some single herb preparations were also included. The labeling of each potential sample was scanned for ingredients listed in table 1 reported to contain mercury, arsenic or lead (Bensky & Gamble, 1993; Kang-Yum & Oransky, 1999; Ministry of Health, 2000; MCA, 2001; Ernst, 2002b; Ministry of Health, 2003; Liu et al, 2008b). We also compared the product name to a list of names of classical formulas for Ayurvedic THPs (Table 2) and a list of classical formulas for Chinese THPs (Table 3) that are reported to include mercury, arsenic or lead compounds. Table 2 was compiled from the official Ayurvedic Formulary published by the Indian government (Ministry of Health, 2000; Ministry of Health, 2003) by selecting from this source the names of formulas for THPs for oral use that included ingredients with lead, mercury or arsenic. Table 3 was compiled from the Pharmacopoeia of the People’s Republic of China (English edition of 1997) by the British Medicine Control Agency supplemented with names of formulas for Chinese THPs which were described in a TCM handbook to contain ingredients with lead, mercury and arsenic (Bensky & Barolet, 1990; MCA, 2001). Also included in table 3 were Chinese THPs reported to contain mercury, arsenic or lead (Kang-Yum & Oransky, 1992; Espinoza et al., 1995; Auyeung et al.,

2002; Mino & Yamada, 2005; Huang et al., 2006; Liu et al., 2008b). THPs with ingredients listed in table 1 or product names listed in tables 2 or 3 were sampled preferentially but other THPs were sampled as well.

5 *ICP-MS determination of metals and metalloids*

A routine method for the determination of metals and metalloids in herbal preparations with Inductively Coupled Plasma Mass Spectrometry (ICP-MS) was developed and validated for several elements including arsenic, lead, and mercury. Routinely cadmium, zinc, copper, nickel, chromium and aluminum were monitored as well. Samples were completely homogenized by grinding them to powder with a grinder (Retsch). To 20 - 100 mg (depending on the elements to be measured) of the powdered sample 3 ml nitric acid (HNO_3 , 65%) and 1 ml hydrogen peroxide (H_2O_2 , 30%) were added. A destruction step was then performed using a microwave oven (Ethos Plus Microwave Labstation, Milestone) in which the samples were treated for 25 minutes at 200°C. The solution produced by the destruction process was then quantitatively transferred with de-ionized water from the destruction vessel to a 50 ml volumetric flask. Before filling the flask to the 50 ml mark with de-ionized water, 500 μl aureumchloride (AuCl , 100 mg/L) solution was added. Throughout the analysis Milli-Q grade de-ionized water was used. The sample solutions were diluted (up to 10000 times) when necessary to fit within the calibration curve and measured with ICP-MS (Thermo Electron PQ Excell) using the 'Collision Cell Technology mode' (CCT-mode) with a helium/hydrogen flow (95/5%). Using this gas mixture in the CCT-mode most interferences were reduced (van der Wielen et al., 2005). In order to test if each destruction vessel was clean prior to use, test runs were performed on each vessel with only 3 ml HNO_3 (65%) and 1 ml H_2O_2 (30%) before each series of samples. This was repeated after each series in order to confirm that no metals or metalloids were left in the vessels. For the in house validation of the method, first the limits of detection and quantification (LOD and LOQ) were determined. The LOD was defined as three times the residual standard deviation of the standard calibration curve. The LOQ was defined as twice the LOD. The range of the calibration curve was used to calculate the range of application. Samples were diluted and reanalyzed when concentrations appeared to exceed the highest concentration of the calibration curve. The accuracy of the method was

determined by analysis of a Certified Reference Material (CRM)(IRMM; BCR 482: trace elements in Lichen). The analytes of this CRM had to be within the 95% confidence interval of the certified values. Furthermore the relative standard deviation (RSD_r) was measured by replicate analysis ($n=6$) of the CRM under repeatability conditions. The RSD_r is a measure of the degree of agreement of results obtained by the same analyst with identical reagents, equipment and instruments within a short period of time under conditions kept as constant as possible. The CRM was also used as quality control sample in each series of measurements. The expanded measurement uncertainty (in mg/kg) was determined as the reproducibility from measurements ($n>10$) of this CRM, analyzed by different persons on different days.

Table 4 lists the method performance characteristics as the LOD, LOQ, range of application, accuracy, RSD_r and the measurement uncertainty (in mg/kg). According to the AOAC guidelines for single laboratory validation of chemical methods for botanicals and dietary supplements, the accuracy has to be between 75 and 120% at the measured concentrations (AOAC, 2002). The values for the accuracy of the method for mercury, arsenic and lead as listed in table 4, fitted well within these limits as did the other elements that can be analyzed with this method. The RSD_r for all elements was found to be below 10% with mercury displaying the highest value of 9.5%. These values are also in accordance with this AOAC program that requires the RSD_r to be below 10% at the measured concentrations. For the elements Al, Ni, Cu and Zn the limits of detection and quantification were about 10 times higher than that of mercury, which has an LOD of 0.03 mg/kg. Addition of AuCl to the sample and flush solutions helped to overcome initial problems with persistent mercury residues in the system because of the capacity of mercury to complex with gold (Falciani et al., 2000).

Estimation of the weekly mercury, arsenic or lead intake and selection of safety limits

At the time of completion of this study neither Dutch nor European food law contained maximum levels for mercury, arsenic or lead in food supplements. We based our enforcement actions therefore on the legal requirement that only safe foods are to be placed on the market. In order to assess the safety of a THP we estimated the associated intake of mercury, lead and mercury and subsequently compared the estimated intakes of these elements to established safety limits. The estimated mercury,

arsenic or lead intake per week was calculated from the analytically determined concentrations of these elements, the unit dose weight and the highest recommended daily dose stated on the label of the THP. In a few cases where no recommended dose could be identified on the label or from other sources a default value was used of, depending on the dose form, 1 pill or 1 g of powder per day. We did not consider background exposure from other sources such as foods, water or ambient air in our risk assessment. For each of these 3 elements we selected an established safety limit by reviewing risk assessments by international and national bodies (Table 5). We preferentially considered safety limits for inorganic mercury, arsenic and lead compounds because available sources on the speciation of these elements in Chinese, Ayurvedic and other Asian THPs consistently indicate that mercury, arsenic and lead are present as inorganic compounds (Aslam et al., 1979; Healy & Aslam, 1986; Bensky & Barolet, 1990; Kang-Yum & Oransky, 1992; Bensky & Gamble, 1993; Kew et al, 1993; Delves & Frost, 1995; Ravinarayan & Skandhan, 1995; Ministry of Health, 2000; Aziz et al., 2002; Ministry of Health, 2003; Mino & Yamada, 2005; Kumar et al., 2006; Sallon et al., 2006; Cooper et al., 2007; Himalaya, 2008). From the selected safety limit we calculated a tolerable weekly intake (TWI) limit for a 60 kg adult. For mercury we selected the TDI for inorganic mercury of 2 µg/kg bw/day set independently by the Dutch National Institute for Public Health and the Environment (RIVM) and the International Program on Chemical Safety (IPCS)(Baars et al., 2001; IPCS, 2003). This TDI is equivalent to a TWI limit of 0.84 mg per week for a 60 kg adult (Table 5). For arsenic we selected the TDI for inorganic arsenic set by RIVM of 1.0 µg/kg bw/day, equivalent to a TWI limit of 0.42 mg per week for a 60 kg adult (Table 5)(Baars et al., 2001). For lead we selected the provisional tolerable weekly intake (PTWI) limit for lead from all sources of 25 µg/kg bw/wk established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), equivalent to a TWI limit of 1.5 mg per week for a 60 kg adult (Table 5)(JECFA, 1993; JECFA, 2000).

In agreement with European Regulation (EC) No. 333/2007 we established for enforcement purposes for mercury, arsenic or lead each, the estimated weekly intake level at which the TWI limit is exceeded beyond reasonable doubt (European Commission, 2007). We derived these VWA action limits by adding to the selected TWI limit for the element, the analytically obtained expanded measurement uncertainty for the estimated weekly intake (in mg/wk). For the estimated lead intake of

a THP, a VWA action limit of 1.85 mg per week was derived. The VWA action limit for the estimated weekly intake of mercury was 1.31 mg per week and for arsenic the VWA action limit was a maximum estimated weekly intake of 0.510 mg per week. Recently the European Commission established for food supplements maximum product levels of 0.10 mg/kg for mercury and 3.0 mg/kg for lead, which will enter into force on the 1st of July 2009 (European Commission, 2008). No limit has yet been proposed for arsenic in food supplements. We also applied these EU maximum levels to our data to estimate the effect of this new legislation on the availability of Asian THPs with mercury or lead on the Dutch market. Furthermore, we applied safety limits used in several pertinent studies on mercury, arsenic or lead in Asian THPs to our data in order to explore how the selection of other relevant limits would have affected the outcome of the study.

Results

Mercury, arsenic or lead contents of THPs

In total 186 (64%) of 292 THPs used in Ayurveda, TCM and TTM contained arsenic, mercury or lead. Figure 1 shows for lead, mercury and arsenic separately, how the THPs are distributed over increasing concentration ranges of these elements. The labeling of less than 20% of the THPs did contain indications that matched an entry of tables 1, 2 or 3, which would suggest the presence of ingredients with mercury, arsenic or lead levels. The remaining THPs were sampled according the general criteria of the defined sampling protocol to test the presence of mercury, arsenic or lead in Asian THPs prevalent on the Dutch market.

Lead was present in 123 (42%) THPs and levels ranged from 0.5 to a maximum of 60,000 mg/kg that was found in the Ayurvedic THP vasant yog. The average lead level in the positive samples was 1,000 mg/kg; the median level was 13 mg/kg and the 95th percentile 573 mg/kg. Mercury was found in 131 (45%) THPs in levels from 0.2 up to 171,000 mg/kg and the highest concentration was found in the Ayurvedic THP yogendra ras. The average mercury level in the positive samples was 11,800 mg/kg, the median level was 50 mg/kg and the 95th percentile was 86,000 mg/kg. In 105 (36%) of the 292 collected THPs arsenic was present in levels ranging from 0.2 up to 89,800 mg/kg, the

latter in the Ayurvedic THP swashanti yog. The average arsenic level in the positive samples was 2,300 mg/kg; the median level was 7.6 mg/kg and the 95th percentile for arsenic of 7,600 mg/kg. In a few cases low levels of cadmium were found but the associated estimated intakes were not above international safety limits (data not shown). Table 6 shows for lead, arsenic and mercury separately the number of Ayurvedic, Chinese and Tibetan THPs in which these elements were detected above the LOQ.

Estimated weekly metal or metalloid intakes in relation to the selected safety limits

In total 64 (22%) of 292 THPs were likely to result in weekly intakes of lead, arsenic or mercury separately or in combination, above the selected TWI limits when used according to recommendations. Levels of these elements in 59 of these 64 THPs would result in intakes that also exceeded the VWA action limits; this signified that in total for 59 (20%) of the 292 THPs the estimated intakes of lead, arsenic or mercury would exceed the selected TWI limits beyond reasonable doubt (Table 7). In total 25 THPs from table 7 carried indications that according to table 1, 2 and 3 suggested that ingredients high in mercury, arsenic or lead, could be present. Use according recommendations of the Ayurvedic THPs 'raja parvatini', 'vasant yog' and 'nature slim' would result in daily doses of lead, mercury and arsenic above all 3 VWA action limits simultaneously.

Figure 2 shows for lead, mercury and arsenic respectively the distribution of THPs over increasing ranges of weekly intake estimates in relation to the individual TWI limits for these elements. The median intake of lead with THPs positive for this metal was 0.11 mg/wk, the median intake of mercury with THPs mercury containing this metal was 0.52 mg/wk and the median arsenic intake with THPs positive for this metalloid was 0.08 mg/wk. The lead intake estimates at proposed dose levels for 10 THPs exceeded the TWI limit of 1.5 mg lead per week (range 1.6 - 192 mg/wk) (Figure 2) and the lead intake estimates for 8 of these also exceeded the VWA action limit of 1.85 mg/wk. Of these 10 THPs, 8 THPs would at their proposed dose levels also result in intakes above TWI limits for arsenic or mercury or both as well. The estimated mercury intake at the proposed dose level of 55 THPs would be above the TWI limit of 0.84 mg inorganic mercury per week (range 0.92 - 1747 mg/wk) (Figure 2) and mercury intake estimates of 50 of these were also above the VWA action

limit of 1.31 mg/wk. Of 26 of these 55 THPs, the intake of arsenic or lead resulting from their proposed dose levels, would also be in excess of the TWI limits for one or both of these two elements. We found 29 THPs where the proposed dose levels would result in arsenic intakes above the TWI limit for arsenic (range 0.44 - 427 mg/wk) (Figure 2) and the proposed dose levels of 26 of these would result in intakes above the VWA action limit for arsenic of 0.510 mg/wk. Additionally, the proposed dose levels of 24 of these 29 THPs would also give rise to mercury or lead intakes in excess of the TWI limits selected for these metals.

Table 8 shows for lead, mercury and arsenic separately, the number of Ayurvedic, Chinese THPs and Tibetan THPs for which use at their proposed dose levels would result in intakes above TWI limits for each of these elements.

In addition to the TWI limits applied above, we also compared our estimated intake data to other relevant safety limits for mercury, arsenic and lead as well as to the maximum levels for lead and mercury in food supplements recently established by the European Commission (European Commission, 2008). Table 9 shows the number of THPs where use according to recommendations would result in intakes of mercury, arsenic and lead above these other safety limits. When the newly defined European maximum levels for lead and mercury were applied, the highest number of exceedances was seen: 101 (82%) of 123 of THPs positive for lead and 130 (99%) of 131 of the products containing mercury were above these limits (Table 9).

Discussion

Mercury, lead and arsenic were detected in 186 (64%) of 292 THPs used in Ayurveda, TCM and TTM sampled in the Netherlands. Use at the proposed dose levels of 59 (20%) of these 292 THPs would result in estimated mercury, arsenic and lead intakes significantly above established safety limits. Furthermore, 82% of the THPs with lead and 99% of the THPs containing mercury exceeded the recently established European maximum product levels for food supplements (Table 9)(European Commission, 2008). Our results are in good agreement with several studies on mercury, arsenic and lead contents of Asian THPs sampled in Western and Asian countries. Saper et al. (2004) found

mercury, arsenic or lead in 20% of 70 Ayurvedic THPs collected in Boston and the estimated intakes of these elements at proposed use levels were all above selected safety limits. Lead was found in 13 THPs (19%), mercury and arsenic both in 6 preparations (9%). Saper et al. used a US Pharmacopoeia specification as a safety limit for lead that was considerably more conservative than the JECFA PTWI for lead (JECFA, 2000) used in our study which would explain why we found a lower percentage of THPs with estimated lead intakes above the TWI limit (Tables 5, 8 and 9). Relative to the results obtained by Saper et al., the subset of Ayurvedic THPs in our study included more THPs (46 (19%) of 242) with estimated mercury intakes above the TWI, which also exceeded the number of THPs with estimated arsenic or lead intakes above the TWI (22 (9%) and 10 (4%), respectively)(Table 8). A similar distribution of mercury, arsenic and lead among Ayurvedic THPs is found in the official Ayurvedic formulary, which includes more formulas with mercury (23%) than arsenic (7,3%) or lead (2,5%)(Ministry of Health, 2000; Ministry of Health, 2003). In 2008 Saper et al. published a study on mercury, arsenic and lead in Ayurvedic THPs purchased via the Internet in 2005. Lead, mercury and arsenic were found in 40 (20.7%) of 193 Ayurvedic THPs manufactured in the US and India. The intake estimates for mercury, arsenic and lead for all THPs that contained these elements, exceeded selected standards (Saper et al., 2008). McElvaine et al. (1990) studied metal and metalloid contents of 22 East Indian THPs sampled in India. Arsenic was found in 9 (41%) of the THPs, lead and mercury were each detected in 14 (64%) of the samples and high cadmium levels were shown in 2 products. Maximum and median arsenic and mercury concentrations, considerably exceeded values found in our study but intake estimates were not provided. Garvey et al. (2001) sampled 54 Chinese and Southeast Asian THPs in Vietnam, Hong Kong and the US and found in 36 (67%) THPs levels of arsenic, lead and mercury that would result in intake estimates above safety limits that were similar to limits selected for our study. In a study by Cooper et al. (2007) at least 160 (65%) of 247 Chinese THPs sampled on the Australian market were contaminated with mercury, lead or arsenic. Background exposure to mercury, arsenic or lead from other foods was subtracted from the TDI, thereby reducing room for mercury, arsenic or lead intake from THPs, and a conservative JECFA PTWI for total mercury (JECFA, 1972) was applied. In total 3% of the Chinese THPs contained mercury, arsenic or lead levels resulting in intakes at the recommended dose that would exceed the selected TDI estimates

by 20-fold to up to 2750-fold (Cooper et al., 2007). In our study 5 (12%) of 42 Chinese THPs could result in estimated mercury, arsenic or lead intakes exceeding safety limits in a range of 1.1-fold to more than 2000-fold (Tables 7 and 8).

In order to identify THPs possibly high in mercury, arsenic or lead beforehand, we screened the labeling for traditional names for Asian THPs or traditional names for ingredients as listed in tables 1-3, which can contain arsenic, lead or mercury. Of the 59 THPs in our study that would result in mercury, arsenic or lead intakes significantly above TWI limits, the labeling of 25 (42%) carried indications from table 1-3, which could suggest high levels of these elements (Table 7). Our sampling protocol, which includes tables 1-3, was therefore helpful in identifying products with significant mercury, arsenic or lead levels which carried traditional product names or ingredients on the labeling. However, it proved not to be effective in identifying high-risk THPs with incomplete ingredient lists or modern product names. Our data suggests that consumers cannot rely on the labeling for avoiding THPs with high amounts of mercury, arsenic or lead and that there is a significant risk of inadvertent exposure to these elements from Asian THPs.

In order to estimate the risks associated with exposure to mercury, arsenic or lead from Asian THPs appropriate safety limits have to be selected. Table 9 shows that the selection of a safety limit considerably influences the outcome of the study which should be considered when interpreting results of studies into mercury, arsenic or lead in THPs. It is pertinent that the differences in toxicity of the various species of an element are taken into account (WHO, 2006). Reports on the speciation of mercury, arsenic or lead in Asian THPs are scarce. Establishing the speciation of elements is less straightforward for Ayurvedic THPs than for Chinese THPs because Ayurvedic THPs are subjected to more rigorous processing steps that include heat treatments. The ultimate mercury, arsenic or lead species in Ayurvedic THPs are therefore more likely to differ from the initial species in the starting materials.

Mercury from Ayurvedic THPs requires special consideration. Purified mercury (parada) is used as the starting material for most mercury containing Ayurvedic THPs. Elemental mercury shows a low oral toxicity when compared to organic and inorganic mercury compounds (ICPS, 2003; Baldwin & Marshal, 1999; Neustadt & Piczenik, 2007). To test if Ayurvedic THPs contained any

residual elemental mercury we performed a pilot study on 23 Ayurvedic THPs in which we had shown mercury to be present. No elemental mercury was detected in these products (data not shown), which indicates that all mercury detected relates to either inorganic or organic mercury. For the preparation of Ayurvedic THPs, mercury is mixed with sulfur until kajjali (black mercuric sulfide, HgS) is formed (Dash, 1986; Ministry of Health, 2000; Ministry of Health, 2003; Himalaya, 2008). Mercury reacts with sulfur, which forms HgS (Fuhrmann et al., 2002; Baughman, 2006). The presence of HgS in Ayurvedic THPs was analytically confirmed for the important Ayurvedic mercury preparation Makaradhwaja (Kumar et al., 2006), which is based on kajjali (Dash, 1986). The preparation was shown to contain 85.3% mercury and 14.2% sulfur matching the stoichiometry of HgS (Kumar et al., 2006). Use of mercuric sulfide in an Indian ethnic remedy in a daily dose of 180-252 mg during 4 weeks resulted in adverse effects consistent with a mercury poisoning (Kew et al, 1993). Inorganic mercury poisonings from oral use of Chinese THPs with calomel (mercurous chloride, Hg_2Cl_2) (Kang-Yum & Oransky, 1992) and cinnabar (used long-term) have been recorded (Liu et al., 2008a). Studies on rats and guinea pigs have shown that mercuric sulfide and its natural form cinnabar are bioavailable and neurotoxic (Chuu et al., 2001; Young et al., 2002; Chuu et al., 2007). Because methylmercury is primarily formed through methylation by microorganisms (Satoh, 2000; ICPS, 2003) and because methylmercury is not used in traditional medicines (Liu et al., 2008a) we considered the presence of this compound in toxicological relevant quantities to be unlikely. The JECFA PTWI for total mercury used by Cooper et al. (2007) is mainly applicable to diets with high consumption of fish with high levels in methylmercury (JECFA, 1989b) and does not necessarily apply to foods high in inorganic mercury (JECFA, 1972). Therefore a TDI for inorganic mercury (Baars et al., 2001; IPCS, 2003) was selected for the risk assessment of mercury from Asian THPs. Although this TDI is based on a NOAEL for inorganic mercuric chloride it also applies to other inorganic mercury compounds such as mercuric sulfide (Baars et al., 2001; IPCS, 2003).

Arsenic is used in Chinese THPs in inorganic form (Bensky & Barolet, 1990; Bensky & Gamble, 1993; Mino & Yamada, 2005; Cooper et al., 2007). In the Ayurvedic Formulary 7% of the formulas contain realgar (manahsila, As_4S_4) and orpiment (talaka, As_2S_3) (Ministry of Health, 2000; Ministry of Health, 2003). From talaka a bhasma is made. Talaka bhasma was reported to contain

As₂S₃ (Kumar et al., 2006). Furthermore arsenic trioxide (As₂O₃) was found in two kushtas from India and Pakistan (Aslam et al., 1979). Arsenic trioxide is significantly more toxic than orpiment and realgar (Liu et al., 2008). Inorganic arsenic compounds are more toxic than several organic arsenic compounds, notably those compounds (eg. arsenobetaine) which can be found in seafood in considerable quantities and which are not of major toxicological concern (IPCS, 2001). A case of arsenic poisoning involving Indian preparations has been reported in Italy (Muzi et al., 2001) and in the UK where use of Indian preparations resulting in intakes of up to 210 mg As₂O₃ per day for more than 4 months, caused symptoms consistent with inorganic arsenic poisoning (Kew et al., 1993). An Indian case of arsenic poisoning showed keratosis after 6 months of use of several Ayurvedic preparations with significant arsenic levels and after 18 months of use non-cirrhotic portal hypertension was diagnosed (Khandpur et al., 2008). Several chronic arsenic poisonings with Chinese THPs have been reported which resulted in cutaneous manifestations such as malignancies and kerotic plaques (Chan, 1994; Wong et al., 1998; Lee et al., 2004; Hanjani et al., 2007). We selected a TDI for inorganic arsenic set by RIVM for the risk assessment of arsenic from Asian THPs. The TDI is based on the JECFA PTWI for inorganic arsenic (JECFA, 1989a) to which an extra uncertainty factor of 2 was applied for observation errors in epidemiological studies (Baars et al., 2001).

Lead in Ayurvedic and Chinese THPs is mostly found in inorganic form. Reported forms are PbS and PbO, which can cause intoxications (Ravinarayan & Skandhan, 1995; Delves & Frost, 1995; ICPS, 1995; Healy & Aslam, 1986). A large number of lead poisonings with Ayurvedic THPs has been reported (Dunbabin et al., 1992; Kew et al, 1993; Sheerin et al., 1994; Keen, 1994; Bayly et al., 1995; Prpic-Majic et al., 1996; van Vonderen et al., 2000; Anderson et al., 2001; Tait et al., 2002; CDC, 2004; Schilling et al., 2004; Kanen & Perenboom, 2005; van Schalkwyk et al., 2006). These reports contradict the claim that lead in Ayurvedic THPs is detoxified. A case of lead poisoning with a Chinese THP has been recorded in Hong Kong (Auyeung et al., 2002). The US Environmental Protection Agency (US EPA) did not establish an oral reference dose (RfD) for lead nor was the Agency for Toxic Substances and Disease Registry (ATSDR) able to derive a minimal risk level (MRL) for lead, because both agencies could not define a clear threshold for some of the health effects linked to exposure to lead (US EPA, 2004; ATSDR, 2007). RIVM set a TDI for lead and lead

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3 compounds which is directly derived from the JECFA PTWI for lead from all sources (Baars et al.,
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5 2001). We selected therefore the PTWI set by JECFA (JECFA, 2000) for the risk assessment of lead
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7 from Asian THPs.
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10 Our study shows that the mercury, arsenic and lead contents of Asian THPs are still a cause for
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12 5 concern and that Asian THPs should routinely be tested for metals and metalloids. The VWA will
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14 continue to monitor metals and metalloids in Asian THPs on the Dutch market and enforce the safety
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16 of these products.
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31 selected Ayurvedic THPs.
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References

AOAC: AOAC Guidelines for Single Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals [Internet]. 2002. Gaithersburg (MD): AOAC International; [cited 2008 October 14]. Available from: http://www.aoac.org/dietsupp6/Dietary-Supplement-web-site/slv_guidelines.pdf

Aslam M, Davis SS, Healy MA. 1979. Heavy metals in some Asian medicines and cosmetics. Public Health. 93:274-284.

ATSDR: Toxicological profile for lead [Internet]. August 2007. Atlanta (GA): Agency for Toxic Substances and Disease Registry, US Public Health Service; [cited 2009 January 10]. Available from: <http://www.atsdr.cdc.gov/toxprofiles/tp13.html>

Auyeung TW, Chang KK, To CH, Mak A, Szeto ML. 2002. Three patients with lead poisoning following use of a Chinese herbal pill. Hong Kong Med J. 8:60-62.

Aziz N, Gilani AH, Rindh MA. 2002. Kushta(s): unique herbo-mineral preparations used in South Asian traditional medicine. Med Hypotheses. 59:468-472

Baars AJ, Theelen RMC, Janssen PJCM, Hesse JM, van Apeldoorn ME, Meijerink MCM, Verdam L, Zeilmaker MJ. Re-evaluation of human-toxicological maximum permissible risk levels [Internet]. 2001. Bilthoven: the Dutch National Institute for Public Health and the Environment; [cited 2009 March 29]. Available from: <http://www.rivm.nl/bibliotheek/rapporten/711701025.html>

Baughman TA. 2006. Elemental Mercury Spills. Environ Health Perspect. 114:147-152.

Bayly GR, Braithwaite RA, Sheehan TM, Dyer NH, Grimley C, Ferner RE. 1995. Lead poisoning from Asian traditional remedies in the West Midlands--report of a series of five cases. *Hum Exp Toxicol.* 14,24-28

5 Bensky D and Barolet R.1990. *Chinese Herbal Medicine: Formulas and Strategies*. Eastland Press, Incorporated. Seattle.

Bensky D and Gamble A. 1993. *Chinese Herbal Medicine: Materia Medica*. Revised edition. Eastland Press, Incorporated, Seattle.

10 Blok-Tip L, Zomer B, Bakker F, Hartog KD, Hamzink M, ten Hove J, Vredenburg M, de Kaste D.

2004. Structure elucidation of sildenafil analogues in herbal products. *Food Addit Contam.* 21:737-748

15 CDC. 2004. Lead poisoning associated with ayurvedic medications--five states, 2000-2003. *MMWR Morb Mortal Wkly Rep.* 53:582-584

Chan TY. 1994. The prevalence use and harmful potential of some Chinese herbal medicines in babies and children. *Vet Hum Toxicol.* 36:238-240

20 Chuu JJ, Liu SH, Lin-Shiau SY. 2001. Effects of methyl mercury, mercuric sulfide and cinnabar on active avoidance responses, Na⁺/K⁺-ATPase activities and tissue mercury contents in rats. *Proc Natl Sci Counc Repub China B.* 25:128-136.

25 Chuu JJ, Liu SH, Lin-Shiau SY. 2007. Differential neurotoxic effects of methylmercury and mercuric sulfide in rats. *Toxicol Lett.* 169:109-120.

Cooper K, Noller B, Connell D, Yu J, Sadler R, Olszowy H, Golding G, Tinggi U, Moore MR, Myers S. 2007. Public health risks from heavy metals and metalloids present in traditional Chinese medicines. *J Toxicol Environ Health. A.* 70:1694-1699.

5 Dash B. 1986. *Alchemy and metallic medicines in Ayurveda*. Concept Publishing Company, New Delhi,.

Delves HT and Frost PG. 1995. Lead preparations in Ayurvedic medicines. *Postgrad Med J.* 71:251.

10 Dunbabin DW, Tallis GA, Popplewell PY, Lee RA. 1992. Lead poisoning from Indian herbal medicine (Ayurveda). *Med J Aust.* 157:835-836.

Ernst E. 2002a. Heavy metals in traditional Indian remedies. *Eur J Clin Pharmacol.* 57:891-896.

15 Ernst E. 2002b. Toxic heavy metals and undeclared drugs in Asian herbal medicines. *Trends Pharmacol Sci.* 23:136-139.

Espinoza EO, Mann MJ, Bleasdel B. 1995. Arsenic and mercury in traditional Chinese herbal balls. *N Engl J Med.* 333:803-804.

20 European Commission. 2007. Commission Regulation (EC) No 333/2007 of 28 March 2007 laying down the methods of sampling and analysis for the official control of the levels of lead, cadmium, mercury, inorganic tin, 3-MCPD and benzo(a)pyrene in foodstuffs. *Off. J. Eur. Union.* L 88/29.

European Commission. 2008. Commission Regulation (EC) No 629/2008 of 2 July 2008 amending Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs. Off J Eur Union. L 173/6.

5 Falciani R, Novaro E, Marchesini M, Gucciardi M. 2000. Multi-element analysis of soil and sediment by ICP-MS after a microwave assisted digestion method. J Anal At Spectrom. 15:561-565.

FSANZ: The 20th Australian total dietary survey [Internet]. 2002. Canberra: Food Standards Australia and New Zealand; [cited 2008 September 28] Available from:

10 www.foodstandards.gov.au/newsroom/publications/20thaustraliantotaldietsurveyjanuary2003/

Fuhrmann M, Melamed D, Kalb PD, Adams JW, Milian LW. 2002. Sulfur Polymer Solidification/Stabilization of elemental mercury waste. Waste Management. 22:327-333.

15 Garvey GJ, Hahn G, Lee RV, Harbison RD. 2001. Heavy metal hazards of Asian traditional remedies. Int J Environ Health Res. 11:63-71.

Hanjani NM, Fender AB, Mercurio MG. 2007. Chronic arsenicism from Chinese herbal medicine. Cutis. 80:305-308.

20 Healy MA and Aslam M. 1986. Lead-containing preparations in the Asian community: a retrospective survey. Public Health. 100:149-151.

Himalaya Herbal Healthcare: 'Shingraf, Hingula', in: Himalaya's Herbs and Minerals [Internet]. 2008.

25 India: The Himalaya Drug Company; [cited 2009 January 18]. Available from:

<http://www.himalayahealthcare.com/aboutayurveda/cahs.htm#shingraf>

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52
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58
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60

Huang RJ, Zhuang ZX, Tai Y, Huang RF, Wang XR, Lee FSC. 2006. Direct analysis of mercury in Traditional Chinese Medicines using thermolysis coupled with on-line atomic absorption spectrometry. *Talanta*. 68:728-734.

5 IPCS. 1995. Inorganic lead; Environmental Health Criteria 165. Geneva: World Health Organization.

IPCS. 2001. Arsenic and arsenic compounds (2nd edition); Environmental Health Criteria 224. Geneva: World Health Organization.

10 IPCS. 2003. Elemental mercury and inorganic mercury compounds: human health aspects; Concise International Chemical Assessment Document 50. Geneva: World Health Organization.

JECFA. 1972. Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyrocarbonate, and octyl gallate; WHO Food Additives Series, No. 4. Geneva World Health Organization. Mercury.

JECFA. 1989a. In: Evaluation of certain food additives and contaminants; WHO Technical Report Series, No. 776, Geneva: World Health Organization. Arsenic; p. 27-28.

20 JECFA. 1989b. Evaluation of certain food additives and contaminants; WHO Technical Report Series, No. 776. Geneva: World Health Organization. Methylmercury; p. 33-34.

JECFA. 1993. Evaluation of certain food additives and contaminants; WHO Technical Report Series, No. 837. Geneva: World Health Organization. Lead; p. 32-35.

25 JECFA. 2000. Evaluation of certain food additives and contaminants; WHO Technical Report Series, No. 896. Geneva: World Health Organization. Lead; p. 81-87.

Johanns ES, van der Kolk LE, van Gemert HM, Sijben AE, Peters PW, de Vries I. 2002. An epidemic of epileptic seizures after consumption of herbal tea. *Ned Tijdschr Geneeskd.* 146:813-816.

Kanen BL, Perenboom RM. 2005. Chronic lead intoxication associated with Ayurvedic medication
5 *Ned Tijdschr Geneeskd.* 149:2893-2896.

Kang-Yum E, Oransky SH. 1992. Chinese patent medicine as a potential source of mercury poisoning.
18 *Vet Hum Toxicol.* 34:235-238.

10 Keen RW, Deacon AC, Delves HT, Moreton JA, Frost PG. 1994. Indian herbal remedies for diabetes
24 as a cause of lead poisoning. *Postgrad Med J.* 70:113-114.

Kew J, Morris C, Aihie A, Fysh R, Jones S, Brooks D. 1993. Arsenic and mercury intoxication due to
31 Indian ethnic remedies. *BMJ.* 306:506-507.

15 Khandpur S, Malhotra AK, Bhatia V, Gupta S, Sharma VK, Mishra R, Arora NK. 2008. Chronic
36 arsenic toxicity from Ayurvedic medicines. *Int J Dermatol.* 47:618-621.

Kumar A, Nair AG, Reddy AV, Garg AN. 2006. Bhasmas: unique ayurvedic metallic-herbal
20 preparations, chemical characterization. *Biol Trace Elem Res.* 109:231-254.

Lee JJ, Kim YK, Cho SH, Park KS, Chung IJ, Cho D, Ryang DW, Kim HJ. 2004. Hemolytic anemia
50 as a sequela of arsenic intoxication following long-term ingestion of traditional Chinese medicine. *J.*
52 *Korean Med Sci.* 19:127-129.

25 Li AM, Chan MH, Leung TF, Cheung RC, Lam CW, Fok TF. 2000. Mercury intoxication presenting
57 with tics. *Arch Dis Child.* 83:174-175.

Liu J, Shi JZ, Yu LM, Goyer RA, Waalkes MP. 2008a. Mercury in traditional medicines: is cinnabar toxicologically similar to common mercurials? *Exp Biol Med*. 233:810-817.

Liu J, Lu Y, Wu Q, Goyer RA, Waalkes MP. 2008b. Mineral arsenicals in traditional medicines: orpiment, realgar, and arsenolite. *J Pharmacol Exp Ther*. 326:363-368.

Martena MJ, van der Wielen JCA, Klerx WNM, de Groot HN, Rietjens IMCM. 2006. Heavy metal ingredients of traditional Asian herbal preparations [abstract]. Abstracts of the Dutch toxicology days, 13th-14th June 2006. *Chem.- Biol Interact*. 161:165-175.

Martena MJ, van der Wielen JCA, van de Laak LFJ, Konings EJM, Groot HN, Rietjens IMCM. 2007. Enforcement of the ban on Aristolochic acids in Chinese traditional herbal preparations on the Dutch market. *Anal Bioanal Chem*. 389:263-275.

McElvaine MD, Harder EM, Johnson L, Baer RD, Satzger RD. 1990. Lead poisoning from the use of Indian folk medicines. *JAMA*. 264:2212-2213.

MCA: Traditional Ethnic medicines: Public health and compliance with medicines law [Internet]. 2001. London: Medicines Control Agency; [cited 2008 September 28]. Available from:

<http://www.escop.com/bhma/bhma/frame.htm>

MHRA: Consumer warning: heavy metals in Ayurvedic herbal medicines [Internet]. 2005. London: Medicines and Healthcare Products Regulatory Agency; [cited 2008 September 28]. Available from:

<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON2014944>

Ministry of Health and Family Welfare, Department of Indian Systems of Medicine and Homoeopathy, Government of India. 2000. The Ayurvedic Formulary of India, Part II. First English edition. Delhi: Controller of Publications.

Ministry of Health and Family Welfare, Department of Indian Systems of Medicine and Homoeopathy, Government of India. 2003. The Ayurvedic Formulary of India, Part I. Second revised English edition. Delhi: Controller of Publications.

Mino Y, Yamada Y. 2005. Detection of high levels of arsenic and mercury in some Chinese Traditional Medicines using x-ray fluorescence spectrometry. *J Health Sci.* 51:607-613.

Moore C, Adler R. 2000. Herbal vitamins: lead toxicity and developmental delay. *Pediatrics.* 106:600-602.

Muzi G, Dell'omo M, Madeo G, Abbritti G, Caroli S. 2001. Arsenic poisoning caused by Indian ethnic remedies. *J Pediatr.* 139:169.

Patwardhan B, Warude D, Pushpangadan P, Bhatt N. 2005. Ayurveda and traditional Chinese medicine: a comparative overview. *Evid. Based Complement. Alternat Med.* 2:465-473.

Prpic-Majic D, Pizent A, Jurasovic J, Pongracic J, Restek-Samarzija N. 1996. Lead poisoning associated with the use of Ayurvedic metal-mineral tonics. *J Toxicol Clin Toxicol.* 34:417-23.

Ravinarayan A, Skandhan KP. 1995. Lead preparations in Ayurvedic medicines. *Postgrad Med. J.* 71: 251.

Rietjens IMCM, Martena MJ, Boersma MG, Spiegelberg W, Alink GM. 2005. Molecular mechanisms of toxicity of important food-borne phytotoxins. *Mol Nutr Food Res.* 49:131-158.

Sallon S, Namdul T, Dolma S, Dorjee P, Dolma D, Sadutshang T, Ever-Hadani P, Bdolah-Abram T, Apter S, Almog S, Roberts S. 2006. Mercury in traditional Tibetan medicine - panacea or problem? Hum Exp Toxicol. 25:405-412.

5 Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Phillips RS. 2004. Heavy metal content of ayurvedic herbal medicine products. JAMA. 292:2868-2873.

Saper RB, Phillips RS, Sehgal A, Khouri N, Davis RB, Paquin J, Thuppil V, Kales SN. 2008. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA. 300:915-923.

Satoh H. 2000. Occupational and environmental toxicology of mercury and its compounds. Ind Health. 38:153-164.

15 Schilling U, Mück R, Heidemann E. 2004. Bleiintoxikation durch Einnahme ayurvedische Arzneimittel. Med Klin. 99:476-480.

Sheerin NS, Monk PN, Aslam M, Thurston H. 1994. Simultaneous exposure to lead, arsenic and mercury from Indian ethnic remedies. Br J Clin Pract. 48:332-333.

20 Tait PA, Vora A, James S, Fitzgerald DJ, Pester BA. 2002. Severe congenital lead poisoning in a preterm infant due to a herbal remedy. Med J Aust. 177:193-195.

Thatte UM, Rege NN, Phatak SD, Dahanukar SA. 1993. The flip side of Ayurveda. J Postgrad Med. 39:179-182, 182a-182b.

US EPA: Lead and compounds (inorganic); Integrated risk information system [Internet]. 2004.

Washington DC: US Environmental Protection Agency; [cited 2009 January 10]. Available from:

<http://www.epa.gov/iris>.

- 5 van Schalkwyk J, Davidson J, Palmer B, Hope V. 2006. Ayurvedic medicine: patients in peril from plumbism. N Z Med J. 119 (1233):65-70.

van Vonderen MG, Klinkenberg-Knol EC, Craanen ME, Touw DJ, Meuwissen SG, De Smet PA.

2000. Severe gastrointestinal symptoms due to lead poisoning from Indian traditional medicine. Am J

- 10 Gastroenterol. 95:1591-1592.

van der Wielen J, Klerx W, in 't Veld P. 2005. Determination of interferences in the analysis of elements in foodstuffs with ICP-MS using Collision Cell Technology (CCT). European Winter Conference on Plasma Spectroscopy; Feb 2005; Budapest, Hungary.

- 15 VWA: VWA waarschuwt voor ayurvedische kruidenpreparaten [Internet]. 2005. Den Haag: Voedsel en Waren Autoriteit; [cited 2008 September 28]. Available from:
http://www.vwa.nl/portal/page?_pageid=119,1639824&_dad=portal&_schema=PORTAL&p_news_item_id=10155

- 20 WHO. 2006. Elemental speciation in human health risk assessment; Environmental health criteria, 234. Geneva: World Health Organization.

- Wong SS, Tan KC, Goh CL. 1998. Cutaneous manifestations of chronic arsenicism: review of
25 seventeen cases. J Am Acad Dermatol. 38:179-185.

Wu TN, Yang KC, Wang CM, Lai JS, Ko KN, Chang PY, Liou SH. 1996. Lead poisoning caused contaminated Cordyceps, a Chinese herbal medicine: two case reports. Sci Total Environ. 182:193-195

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46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Young YH, Chuu JJ, Liu SH, Lin-Shiau SY. 2002. Neurotoxic mechanism of cinnabar and mercuric sulphide on the vestibulo-ocular reflex system of guinea pigs. *Toxicol Sci.* 67:256-63.

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Figure legends

Figure 1. Concentrations of lead, mercury and arsenic in THPs. n.d: not detected

- 5 Figure 2. Estimated weekly intake of lead, mercury and arsenic resulting from intake of THPs at their proposed use levels. 'TWI' refers to the tolerable weekly intake limit for each element; for lead the TWI is 1.5 mg/wk, for mercury 0.84 mg/wk and for arsenic 0.42 mg/wk. n.d: not detected

Tables. Martena et al.: [Monitoring of mercury, arsenic and lead in traditional Asian herbal preparations on the Dutch market and estimation of associated risks](#)

Deleted: Levels of heavy metals in selected traditional Asian herbal preparations on the Dutch market and estimation of associated risks.

Table 1. Traditional names of [lead, mercury and arsenic](#) preparations used as ingredients of Asian THPs.

Deleted: heavy metal

Element	Pharmaceutical or traditional names of preparation	Synonyms and related preparations or compounds
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Deleted: Heavy

Deleted: metal

Deleted: metal containing ingredient

Lead	lithargyrum (lead monoxide)	A: girisindura, litharge, mrddara srnga, mrddarasrnga, muddarasankha, sindura
		C: mi tuo seng
	A: naga bhasma	A: ahi, bhujagalauiha, sisaka,
Mercury	A: parada (purified mercury)	A: chapala, haraja; isa, mrtasuta, rasa, rasa
		sindura, rasaraja rasendra, rasesa, rasesvara, rasottama, suddhasuta, suta, sutaka,
	cinnabar (red mercury sulfide)	A: aruna, caliya, hingula, hingulotthaparada, hingula sambhava suta, suddha hingula
		C: zhu sha, chen sha, dan sha
	calomel (mercurous chloride)	C: qing fen, shui yin fen, gong fen, chen fen
Arsenic	hydrargyri oxydum rubrum (red mercury oxide)	
	orpiment (arsenic trisulfide)	A : ala, haratala, haritala, tala, talaka
		C : cihuang
	realgar (arsenic sulfide or arsenic disulfide)	A: manahsila, manayola, sila,
		C: xiong huang, xiong jing, yao huang
	arsenolite (white arsenic or arsenic trioxide)	A: gauripasana, malla, svetamalla
		C: pishi
A: traditional name used in Ayurveda		

C: traditional name used in TCM

References: (Bensky & Gamble, 1993; Kang-Yum & Oransky, 1999; Ministry of Health, 2000; MCA, 2001; Ernst, 2002b; Ministry of Health, 2003; Liu et al, 2008b)

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Table 2. Formulas for Ayurvedic THPs for oral use possibly containing mercury, arsenic or lead.

Ayurvedic THP	Synonyms	Ayurvedic THP	Synonyms	Ayurvedic THP	Synonyms
agnitundivati	angitundi vati	caturbhuj rasa	chaturbhuj rasa	kasturyadi vayu gutika	
ajirna kantaka rasa		caturmukha rasa	chaturmukh ras	kravyada rasa	
amavatari rasa	amavatari ras; amvatari ras	cintamanicaturmukha rasa		krmi kuthara rasa	krimi kuthar rasa
amlapittantaka rasa	amlapittantka rasa	ekangavira rasa	kangveer ras; ekangvir ras	krmimudgara rasa	krimimudgar ras
anandabhairava rasa	anand bhairav ras; anandbhairav ras	gaganasundara rasa		kumarakalyana rasa	kumarkalyan rasa
arogyavardhini gutika		gandamala kandana rasa		laghvananda rasa	
arsakuthara rasa	arsh kuthar ras ;arsha kuthar rasa	gandhaka vati	gandhak bati (raj bati)	lakanatha rasa	
astaksari gutika		garbha cintamani rasa		laksminarayana rasa	laxminarayan rasa
asvakancuki rasa	ashwakanchuki ras	garbhapala rasa	garbhapal ras	laksmivilasa rasa	laxmivilas ras; laxmi vilas rasa
balarka rasa	balark rasa	gorocanadi vati	gorochandi vati	lauha parpati	
bola parpati	bol parpati	grahani kapata rasa	grahani kapat ras	lila vilasa rasa	lilavilas rasa
brhadagnikumara rasa		guducyadi modaka		mahagandhaka vati	
brhanmaricadya taila		gulma kalanala rasa	gulma kalanal ras	maha jvarankusa rasa	mahajwarankush ras; mahajvarankush rasa
brhat candrodaya		haritala bhasma	harital bhasma	maha laksmivilasa rasa	mahalaxmi vilas rasa; mahalaxmivilas ras;
makaradhvaja		hemagarbha pottali rasa			mahalakshmi vilas ras
brhat garbhacintamani rasa	brihat garbhachintamani rasa; garbha chintamani ras vrihat brihat kasturi bhairav rasa	hemanatha rasa	hemnath ras	mahatarunarka rasa	
brhat kasturibhairava rasa		hingulesvara rasa			
brhat nrpavallabha rasa		hiranya garbha pottali rasa		maha vata vidhvamsana rasa	mahavatvidhvasan ras; mahavatvidhvasan rasa;
brhat purnacandra rasa	brihat purnachandra rasa	hrdanyarnava rasa	hridayarnava ras		mahavat vidhwans ras
brhat sarvajvarahara lauha	sarvajwarhar loha br.	icchabhedi rasa	ichhabhedi ras (jaypal yukta)	maha vatagajankus a rasa	
brhat vangesvara rasa	bangeshwar ras brihat	jalodarari rasa		maha yogaraja guggulu	maha yograj guggul
brhat vatacintamani rasa	brihat vata chintamani; brihat vatchintamani rasa	jvaraghnai gutika			
brhat vidyadharabhra rasa		jvarankusa rasa (ka)		makara dhvaja	makardhwaj; makardhvaj rasa
brhat visamajvarantaka		jvaryabhra		mallasindura	mallasindur
lauha		kalakuta rasa		manikya rasa	
brhatcchrngarabhra rasa		kanakasundara rasa		manmathabhra rasa	
candrakala rasa	chandrakala ras (Tamra Yukta)	kancanabhra rasa	khantavallabha rasa	maricadya taila	
candramrta rasa	chandramrit ras	kantavallabha rasa	karpara rasa	mrtyunjaya rasa	mrityunjai ras
candramsu rasa		kasisadi ghrta	karpur ras	muktapancamrta rasa	mukta panchamrit ras; moti
		kasturi bhairava rasa	kastoori bhairav ras		

	yukt	samirapannaga rasa	samirpannag rasa	tamra parpati	
naga bhasma	nag bhasma	sankha vati	shankhavati; shankh vati	tarakesvara rasa	
naraca rasa		saubhagya vati	saubhagya bati	tarunarka rasa	
navaratnarajamrganka rasa		siddhapranes vara rasa	siddhapraneshwar rasa	tribhuvanakirti rasa	tribhuvankirti
nidrodya rasa		sirah suladi vajra rasa	shirahsuladrivajara ras	trivanga bhasma	tribanga bhasma
nityananda rasa		smrti sagara rasa	smritisagar ras; smriti sagar rasa	trivikrama rasa	
nrpativallabha rasa	nripatiballabha ras			unmadagajakesari rasa	
pancamrta lauha guggulu		sri jayamangala rasa		vajrakapata rasa	
pancamrta parpati	panchmrita parpati	sri ramabana rasa		vanga bhasma	
pancanana rasa		srinrpativallabha rasa		varisosana rasa	
piyusavalli rasa	piyushvali ras	srngarabhra rasa	shringarabhra ras	varja bhasma	
prabhakara rasa		sucikabharana rasa		vasanta malati rasa	
pradarantaka lauha	pradarantak lauh	sukramatrka vati	shukramatrika vati	vasanta tilaka rasa	
pradarantaka rasa	pradarantak rasa	sulavajrini vatika	shoolvarjini vati	vasantakusumakara rasa	vasant kusumakar rasa
pratapalankesvara rasa	prataplankeshwar	sutasekhara rasa	soothashekara; sutshekhar rasa; sutsjekhar rasa	vata gajankusa rasa	vatagajankush ras; vatgajankush rasa
purnacandra rasa	purnachandra ras		sutikabharan ras		
puspadhanva rasa	pushpadhanwa	sutikabharana rasa		vatagnikumara rasa	
putapakva visama jvarantaka lauha		svacchanda bhairava rasa		vatakulantaka rasa	vatkulantak ras; vatakulantak ras
rajamrganka rasa		svalpanayika curna			
rajata bhasma		svarna bhasma	swarna bhasma	vataraktantaka rasa	
rasa parpati	ras parpati	svarna parpati	swarna parpati	vatari rasa	vatari ras
rasakarpura		svarnabhupati rasa		vatavidhavamsana rasa	
rasamanikya	rasa manikya	svarnasindura		vidanga lauha	
rasapuspa		svarnavanga		yakrdari lauha	
rasaraja rasa	ras raj ras; rasraj rasa	svasa kasa cintamani rasa	shawsa kasa chintamani; swasakas chintamani rasa	yakrtplihari lauha	yakritplihari loha
rasasindura	rasa sindur	svasakuthara rasa	swas kuthar ras; swasa kuthara ras; shwas kuthar rasa	yogendra rasa	
ratnagiri rasa		tamra bhasma			

References: Ministry of Health, 2003; Ministry of Health, 2000

Table 3. Formulas for Chinese THPs for oral use possibly containing mercury, arsenic or lead.

Product Name	Toxic substance	Product Name	Toxic substance	Product Name	Toxic substance
Ailing Yihao #	Arsenolite	Jierezhenluesan ^s	Cinnabar	Shixiang Fansheng Wan	Cinnabar (+ <i>Aristolochia</i> Radix)
Angong Niu Huang San, -Wan */**/ ^{ss}	Cinnabar, Realgar	Jiusheng San	Calomel, Hydrargyri Oxydum Rubrum	Shugan Wan	Cinnabar
An Shen Bu Nao Pian ** (Ansenpunaw tablets)	Cinnabar	Jiuyi San	Hydrargyri Oxydum Rubrum	Shuzheng Pian	Cinnabar, Realgar
Bai Zi Yang Xin Wan **	Cinnabar	Jufangniu Huang-qingxinwan ^s	Cinnabar, Realgar	Suhexiang Wan/ Su He Xian Wan*/**	Realgar
Baochi San	Cinnabar	Jufang Zhibao San	Cinnabar, Realgar	Ta Huo Lo Tan ^{ss}	high mercury and arsenic contents reported ^{ss}
Baochiwanying-san ^s	Cinnabar	Liushenwan ^s / Liu Shen Wan*	Realgar	Tianwang Buxin Wan	Cinnabar
Baolong Wan	Cinnabar	Meihua Dianshe Wan	Cinnabar, Realgar	Tiewadan ^s	Cinnabar
Bao Ning Dan ***	Cinnabar	Niu Huang Baolong Wan	Cinnabar, Realgar	Tse Koo Choy**	Calomel
Bao Ying Dan**	Cinnabar	Niu Huang Cheng Qi Tang*	Cinnabar, Realgar	Tsai Tsao Wan ^{ss}	high mercury and arsenic contents reported ^{ss}
Bingpen San	Cinnabar	Niu Huang Chiang Ya Wan	high mercury and arsenic contents reported ^{ss}	Tzuhsueh Tan (Zi Xue Dan)**	Cinnabar
Biwen San	Cinnabar	Niu Huang Ching Hsin Wan	high mercury and arsenic contents reported ^{ss}	Wanshi Niu Huang Qingxin Wan/ Wan Shi Niu Huang	Cinnabar
Bushen Yiniao Pian	Cinnabar	Niu Huang Jiedu Pian	Realgar	Qing Xin Wan**	
Chunyang Zhengqi Wan	Cinnabar, Realgar (+ <i>Aristolochia</i> Radix)	Niu Huang Qianjin San	Cinnabar	Watermelon frost (Xi Gua Shuang)**	Cinnabar
Ci Zhu Wan*/ **	Cinnabar	Niu Huangqingfei-san ^s	Cinnabar, Realgar	Xiangsu Zhengwei Wan	Cinnabar
Da Huo Luo Wan ^{ss}	high mercury content reported ^{ss}	Niu Huang Qing Xin Wan*	Cinnabar, Realgar	Xiao'er Baishou Wan	Cinnabar
Da qili San	Cinnabar ^{sss}	Niu Huang Zhenjing Wan	Cinnabar, Realgar	Xiao'er Huadu San	Realgar
Dendrobium Moniliforme	high mercury content reported ^{ss}	Peaceful**	Cinnabar	Xiao'er Jindan Pian	Cinnabar (+ <i>Aristolochia</i> <i>manshuriensis</i>)
Night Sight Pills ^{ss}	Cinnabar	Pinggan Shuluo Wan	Cinnabar	Xiao'er Jingfeng San	Cinnabar, Realgar
Ding Xian Wan*	Cinnabar	Po Lung Yuen Med. Pills **	Cinnabar	Xiao'erqifengsan	Cinnabar
Ershiwuwei Shanhu Wan	Cinnabar	Qianjinsan ^s	Cinnabar	Xiao'er Qingre Pian	Cinnabar, Realgar
Ershiwuwei Songshi Wan	Cinnabar	Qi Li San*/**	Cinnabar	Xiao'erqiyingwan ^s	Cinnabar (arsenic also detected ^s)
Feierwanyaopian ^s	Cinnabar	Qizhen Wan	Cinnabar, Realgar	Xiao'er Zhibao Wan	Cinnabar, Realgar
Geng Yi Wan*	Cinnabar	Renqing Changjue	Cinnabar	Xi Gua Shuang (Watermelon frost)	Cinnabar
Hongling San	Cinnabar, Realgar	Renqing Mangjue	Cinnabar	Yatong Yili Wan	Cinnabar, Realgar
Hua Chong Wan	Red lead oxide	San Li Hui Chun Dan**	Cinnabar	Yinianjin	Cinnabar
Hui Chun Dan*	Cinnabar	Shayao	Cinnabar, Realgar		
Hu Po Bao Long Wan (Po Lung Yuen Med. Pills) **	Cinnabar	She Dan Chen Pi San**	Cinnabar		
Jian Nao Wan (healthy brain pills)**	Cinnabar	Sheng Tie Luo Yin			

Yingerbaofeining ^s	Cinnabar
Yingerle ^s	Cinnabar
Yixian Wan	Cinnabar, Realgar
Yi Yuan San*	Cinnabar
Zaizao Wan	Cinnabar
Zhi Bao Dan	Cinnabar, Realgar
Zhou Che Wang*	Calomel
Zhuhuang Chuihou San	Realgar
Zhu Sha An Shen Wan*/** (Cinnabar sedative pill)	Cinnabar
Zijin Ding/ Zi Jin Ding**	Cinnabar, Realgar
Zixue	Cinnabar
Zi Xue Dan*/** (Tzuhsueh Tan)**	Cinnabar

References: MCA, 2001; *Bensky & Barolet, 1990; **Kang-Yum & Oransky, 1992; *** Auyeung et al., 2002; ^sMino & Yamada, 2005; ^{\$\$}Espinoza et al., 1995; ^{\$\$\$}Huang et

al., 2006; # Liu et al., 2008b

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Table 4. Characteristics (limit of detection (LOD), limit of quantification (LOQ), range of application, accuracy and expanded measurement uncertainty) of the analytical method for Pb, As and Hg determined by in house validation.

Element	LOD	LOQ	Range of application	Accuracy ¹	RSD _r ²	Expanded Measurement
	(mg/kg)	(mg/kg)	(mg/kg)	(%)	(%)	Uncertainty ³ (mg/kg)
Pb	0.18	0.36	0.25 – 12.5	103	5.1	3.4 (at level of 37.3 mg/kg)
Hg	0.03	0.06	0.25 – 12.5	99	9.5	0.047 (at level of 0.549 mg/kg)
As	0.06	0.13	0.25 – 12.5	96	2.1	0.09 (at level of 0.89 mg/kg)

¹: Accuracy has to be between 75 and 120% (AOAC, 2002)

²: Relative Standard Deviation (RSD_r) may not exceed 10% (AOAC, 2002)

³: The expanded measurement uncertainty (mg/kg) was calculated as the reproducibility at the concentration level of the CRM.

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Table 5. Safety limits for lead, mercury and arsenic.

Element	Safety limit	Safety limit set by	Safety limit set for	Tolerable weekly intake (mg/wk)*
Lead	4.5 µg/d	US Pharmacopeia-	lead from a daily dose	0.0315
		specification ¹	of calcium carbonate	
	25 µg/kg bw/wk	JECFA-PTWI ²	lead from all food sources	1.5
Mercury	0.3 µg/kg bw/d	US EPA-RfD ³	mercuric chloride	0.126
	5 µg/kg bw/wk	JECFA-PTWI ⁴	total mercury from diets high in methylmercury	0.3
	2 µg/kg bw/d	IPCS-TDI ⁵ /RIVM-TDI ⁶	inorganic mercury	0.84
Arsenic	0.3 µg/kg bw/ d	US EPA-RfD ³	inorganic arsenic	0.126
	1.0 µg/kg bw/d	RIVM-TDI ⁶	inorganic arsenic	0.42
	15 µg/kg bw/wk	JECFA-PTWI ⁷	inorganic arsenic	0.90
	3 µg/kg bw/d	ANZFA-TDI ⁸	inorganic arsenic	1.26

* Calculated for a 60 kg adult

References: ¹(Saper et al., 2004), ²(JECFA, 2000), ³(US EPA, 2006), ⁴(JECFA, 1989b), ⁵(IPCS, 2003), ⁶(Baars et al., 2001), ⁷(JECFA, 1989a), ⁸(FSANZ, 2002)

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Table 6. Number of Ayurvedic, Chinese and Tibetan THPs with ~~lead, mercury or arsenic~~ above the limit of quantification.

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	# of Ayurvedic THPs	# of Chinese THPs	# of Tibetan THPs
Total of the THP type sampled	242	42	8
Lead above LOQ*	105	13	5
Mercury above LOQ	117	8	6
Arsenic above LOQ	85	15	5
Total of THPs with at least one element above LOQ	161	19	7

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*LOQ: Limit of quantification.

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Table 7. Asian THPs resulting in estimated lead, mercury or arsenic intakes significantly above one or more TWI limits.

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Asian THP	Type of Asian THP*	Arsenic	Mercury mg/wk	Lead
Abhrak Bashma	A	0.82	n.d.	1.3
Abhrak Bhasma	A	1.0	n.d.	1.6
Agni Vati	A	n.d.	72	n.d.
Amrit Prash	A	0.1	5.1	0.04
Amrit Ras	A	1.8	377	0.27
Arjuna Hepatone	A	n.d.	198	1.0
Arogya Vardhini Vati	A	n.d.	338	n.d.
Arogyavardhini Vishisht	A	0.04	1.9	0.21
Ayfer	A	0.05	0.12	4.0
Ayu-Hirakam	A	0.21	2.6	0.14
Bat Chintamani	A	2.2	471	0.26
Bo Zi Yang Xin Wan	C	n.d.	1473	n.d.
Chandraprabha	A	0.07	n.d.	15
Diabetomed	A	1.4	3.5	0.41
Ding Xin Wan	C	0.44	430	1.3
Ere Forte	A	n.d.	12	0.34
Femi-Smlin	A	7.5	0.73	0.33
Gandhadi Yog	A	n.d.	11	n.d.
Ghandrams Ras	A	n.d.	132	0.14
Guggulu	A	0.38	7.9	3.1
Gurgum-8	T	2.9	317	0.04
Guyu Depak	T	0.47	192	0.1
Guyu Depak	T	0.94	239	0.15
Heartina	A	262	340	n.d.
Herba Figura	A	0.07	2.3	0.07
Herbo Gastrol	A	n.d.	14	0.33
Herbogastrol	A	n.d.	12	0.23
Herbogastrol	A	n.d.	27	n.d.
Hridaya Chintamani	A	2.6	396	n.d.
Jeevani Vati	A	0.22	173	n.d.
Kamachudamani Ras	A	7.7	22	0.27
Liv.52	A	n.d.	n.d.	2.6
Luxmi Vilas Classic	A	0.02	138	0.05
Maha Manjishtadi Ghan Vati	A	0.04	4.2	0.09

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Maha Ras Guggul	A	1.0	1.2	0.03
Mahabatbiddhonsan Ras	A	0.08	69	78
Makar Wazra	A	5.0	903	n.d.
Mutik-25	T	0.53	146	n.d.
Natureslim	A	79	111	192
Pesin	A	0.9	923	0.07
Raja Parvartini	A	2.2	7.2	5.4
Ras Yog	A	0.04	92	n.d.
Ru Pi Xiao Pian	C	1.1	n.d.	n.d.
Sanjiwani	A	427	n.d.	n.d.
Shatavari	A	1.3	2.4	0.14
Shingorabrak	A	n.d.	162	n.d.
Shringrabhra	A	0.8	20	0.12
Shringrabhra	A	n.d.	26	1.2
Sirshool Vajraras	A	0.05	299	1.1
Swas Kuthar Ras	A	66	65	0.11
Swashanti Yog	A	200	118	n.d.
Sworna Yog	A	1.5	70	n.d.
Tianwang Buxin Wan**	C	n.d.	24	0.17
Triyog Misran	A	n.d.	71	n.d.
Ulceromed	A	0.03	22	0.10
Vasant Yog	A	0.60	57	105
Yogendra Ras	A	0.06	274	0.18
Yograj Guggulu	A	0.08	1.4	1.6
Zhui Feng Tou Gu	C	5.1	1747	0.67

Note: Estimated element intake values in bold are above the VWA action limit for that element at the proposed use level; values in italics are between the TWI limit and the VWA action limit.

n.d.: not detected.

* THP types sampled: 'A' for Ayurvedic THPs, 'C' for Chinese THPs, 'T' for Tibetan THPs

** The daily dose assumed to be 1 pill (0.195 g)

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Table 8. Number of Ayurvedic, Chinese and Tibetan THPs where use at the proposed dose levels results in lead, mercury or arsenic intakes above TWI limits.

	# of Ayurvedic THPs	# of Chinese THPs	# of Tibetan THPs
Total of THP in study	242	42	8
Lead intake above TWI	10	n.a.	n.a.
Mercury intake above TWI	46	5	4
Arsenic intake above TWI	22	3	4
Total of THPs with at least one <u>element</u> above TWI	50	5	4

n.a.: not applicable.

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Table 9. Lead, mercury and arsenic intakes with THPs compared to various safety limits for these elements and EU maximum product levels for lead and mercury.

<u>Element</u>	# of THPs	# of THPs with positive for <u>element</u> intakes or <u>element</u> level above limit*	Risk assessment or risk management body responsible for limit and type of limit	Limit recently applied for Asian THPs in:
Lead	123	10	JECFA-PTWI ¹	this study; Cooper et al., 2007
		99	US Pharmacopeia-specification ²	Saper et al., 2004
		101	EU-maximum level ³	this study
Mercury	131	55	RIVM-TDI ⁴ /IPCS-TDI ⁵	this study
		68	JECFA-PTWI ⁶	Cooper et al., 2007
		91	US EPA-RfD ⁷	Saper et al., 2004
		130	EU- maximum level ³	this study
Arsenic	105	29	RIVM-TDI ⁴	this study
		17	ANZFA-TDI ⁸	Cooper et al., 2007
		21	JECFA-PTWI ⁹	Mino and Yamada, 2005
		39	US EPA- RfD ⁷	Saper et al., 2004

* Calculated either by comparing the estimated intake of a element resulting from the recommended use of the THP with the safety limit referred to in the next column calculated for a 60 kg adult or by comparing a maximum product level to the element concentration.

References: ¹(JECFA, 2000), ²(Saper et al., 2004), ³(European Commission, 2008), ⁴(Baars et al., 2001), ⁵(IPCS, 2003), ⁶(JECFA, 1989b), ⁷(US EPA, 2006), ⁸(FSANZ, 2002). ⁹(JECFA, 1989a)

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