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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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3 **Monitoring of mercury, arsenic and lead in traditional Asian herbal**
4 **preparations on the Dutch market and estimation of associated risks**
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24
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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-Maijc 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.,

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3 1993; Ravinarayan & Skandhan, 1995; Ministry of Health, 2000; Ministry of Health, 2003; Kumar et
4 al., 2006). Comparable preparations called kushtas and parpams are in use in Unani-Tibb and Siddha,
5
6 respectively (Bajaj & Vohora, 2000; Aziz et al., 2002).
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9
10 Metals and metalloids can exist in different defined chemical species and the toxicity of these
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12 5 species can vary significantly (WHO, 2006). Available reports consistently point to the presence of
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14 inorganic metal or metalloid compounds in Chinese, Tibetan and Indian THPs including Ayurvedic
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16 THPs. Naga bhasma, a widely used Ayurvedic lead preparation (Ministry of Health, 2000), contains
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18 lead sulfide (PbS); other lead preparations contain lead oxide (PbO) or lead sulfate (PbSO₄)
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20 (Ravinarayan & Skandhan, 1995; Kumar et al., 2006). In TCM, lithargyrum or 'mi tuo seng' (PbO) is
21
22 10 used (Bensky & Barolet, 1990). Important Ayurvedic mercury preparations are 'parada' (purified
23
24 mercury), 'hingula' (cinnabar, HgS), 'kajjali' (HgS) and 'makaradhvaja' (HgS)(Kumar et al., 2006;
25
26 Himalaya, 2008). In TTM processed mercury preparations (tsothel) are used as well, which mainly
27
28 consist of mercuric sulfide (HgS) and smaller amounts of mercuric sulfite (HgSO₃) and mercuric
29
30 sulfate (HgSO₄) (Sallon et al., 2006). In TCM mercury is used as cinnabar (zu sha) and as calomel
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32
33 15 (qing fen, Hg₂Cl₂) (Bensky & Barolet, 1990; Kang-Yum & Oransky, 1992; Bensky & Gamble, 1993;
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35 Mino & Yamada, 2005; Cooper et al., 2007). In both Chinese and Ayurvedic THPs, realgar (As₄S₄),
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37 orpiment (As₂S₃) and arsenolite (As₂O₃) are used but in Ayurveda these minerals are processed before
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39 use (Bensky & Barolet, 1990; Bensky & Gamble, 1993; Mino & Yamada, 2005; Cooper et al., 2007;
40
41 Liu et al., 2008b). In certain kushtas (used in Unani-Tibb) As₂O₃ was found but kusthas can contain
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44 20 other inorganic arsenicals as well (Aslam et al., 1979; Kew et al., 1993; Aziz et al., 2002).
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47 In 2004 the Dutch Food and Consumer Product Safety Authority (VWA) received reports of
48
49 two cases of lead poisoning linked to the use of Ayurvedic THPs from, respectively, India and Nepal
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51 (VWA, 2005; Kanen & Perenboom, 2005). These cases prompted the VWA to intensify investigations
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53 into metal and metalloid contents of Asian THPs. The objective of this investigation was to study the
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55 25 metal and metalloid contents of Asian THPs on the Dutch market and assess the related risks by
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57 comparing the estimated metal and metalloid intake resulting from use at the proposed dose levels to
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59 established toxicological safety limits. The current report presents the results of this study.
60

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.,

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3 2002; Mino & Yamada, 2005; Huang et al., 2006; Liu et al., 2008b). THPs with ingredients listed in
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5 table 1 or product names listed in tables 2 or 3 were sampled preferentially but other THPs were
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7 sampled as well.
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10 5 *ICP-MS determination of metals and metalloids*

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12 A routine method for the determination of metals and metalloids in herbal preparations with
13
14 Inductively Coupled Plasma Mass Spectrometry (ICP-MS) was developed and validated for several
15
16 elements including arsenic, lead, and mercury. Routinely cadmium, zinc, copper, nickel, chromium
17
18 and aluminum were monitored as well. Samples were completely homogenized by grinding them to
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20 powder with a grinder (Retsch). To 20 - 100 mg (depending on the elements to be measured) of the
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22 powdered sample 3 ml nitric acid (HNO₃, 65%) and 1 ml hydrogen peroxide (H₂O₂, 30%) were added.
23
24 A destruction step was then performed using a microwave oven (Ethos Plus Microwave Labstation,
25
26 Milestone) in which the samples were treated for 25 minutes at 200°C. The solution produced by the
27
28 destruction process was then quantitatively transferred with de-ionized water from the destruction
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30 vessel to a 50 ml volumetric flask. Before filling the flask to the 50 ml mark with de-ionized water,
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32 500 µl aureumchloride (AuCl₃, 100 mg/L) solution was added. Throughout the analysis Milli-Q grade
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34 de-ionized water was used. The sample solutions were diluted (up to 10000 times) when necessary to
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36 fit within the calibration curve and measured with ICP-MS (Thermo Electron PQ Excell) using the
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38 'Collision Cell Technology mode' (CCT-mode) with a helium/hydrogen flow (95/5%). Using this gas
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40 mixture in the CCT-mode most interferences were reduced (van der Wielen et al., 2005). In order to
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42 test if each destruction vessel was clean prior to use, test runs were performed on each vessel with only
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44 3 ml HNO₃ (65%) and 1 ml H₂O₂ (30%) before each series of samples. This was repeated after each
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46 series in order to confirm that no metals or metalloids were left in the vessels. For the in house
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48 validation of the method, first the limits of detection and quantification (LOD and LOQ) were
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50 determined. The LOD was defined as three times the residual standard deviation of the standard
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52 calibration curve. The LOQ was defined as twice the LOD. The range of the calibration curve was
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54 used to calculate the range of application. Samples were diluted and reanalyzed when concentrations
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56 appeared to exceed the highest concentration of the calibration curve. The accuracy of the method was
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3 determined by analysis of a Certified Reference Material (CRM)(IRMM; BCR 482: trace elements in
4 Lichen). The analytes of this CRM had to be within the 95% confidence interval of the certified
5 values. Furthermore the relative standard deviation (RSD_r) was measured by replicate analysis ($n=6$)
6 of the CRM under repeatability conditions. The RSD_r is a measure of the degree of agreement of
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12 5 results obtained by the same analyst with identical reagents, equipment and instruments within a short
13 period of time under conditions kept as constant as possible. The CRM was also used as quality
14 control sample in each series of measurements. The expanded measurement uncertainty (in mg/kg)
15 was determined as the reproducibility from measurements ($n>10$) of this CRM, analyzed by different
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21 persons on different days.

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23 10 Table 4 lists the method performance characteristics as the LOD, LOQ, range of application,
24 accuracy, RSD_r and the measurement uncertainty (in mg/kg). According to the AOAC guidelines for
25 single laboratory validation of chemical methods for botanicals and dietary supplements, the accuracy
26 has to be between 75 and 120% at the measured concentrations (AOAC, 2002). The values for the
27 accuracy of the method for mercury, arsenic and lead as listed in table 4, fitted well within these limits
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34 15 as did the other elements that can be analyzed with this method. The RSD_r for all elements was found
35 to be below 10% with mercury displaying the highest value of 9.5%. These values are also in
36 accordance with this AOAC program that requires the RSD_r to be below 10% at the measured
37 concentrations. For the elements Al, Ni, Cu and Zn the limits of detection and quantification were
38 about 10 times higher than that of mercury, which has an LOD of 0.03 mg/kg. Addition of AuCl to the
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44 20 sample and flush solutions helped to overcome initial problems with persistent mercury residues in the
45 system because of the capacity of mercury to complex with gold (Falciani et al., 2000).
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51 *Estimation of the weekly mercury, arsenic or lead intake and selection of safety limits*

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53 At the time of completion of this study neither Dutch nor European food law contained maximum
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55 25 levels for mercury, arsenic or lead in food supplements. We based our enforcement actions therefore
56 on the legal requirement that only safe foods are to be placed on the market. In order to assess the
57 safety of a THP we estimated the associated intake of mercury, lead and mercury and subsequently
58 compared the estimated intakes of these elements to established safety limits. The estimated mercury,
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3 arsenic or lead intake per week was calculated from the analytically determined concentrations of
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5 these elements, the unit dose weight and the highest recommended daily dose stated on the label of the
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7 THP. In a few cases where no recommended dose could be identified on the label or from other
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9 sources a default value was used of, depending on the dose form, 1 pill or 1 g of powder per day. We
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11 did not consider background exposure from other sources such as foods, water or ambient air in our
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13 risk assessment. For each of these 3 elements we selected an established safety limit by reviewing risk
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15 assessments by international and national bodies (Table 5). We preferentially considered safety limits
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17 for inorganic mercury, arsenic and lead compounds because available sources on the speciation of
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19 these elements in Chinese, Ayurvedic and other Asian THPs consistently indicate that mercury,
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21 arsenic and lead are present as inorganic compounds (Aslam et al., 1979; Healy & Aslam, 1986;
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23 Bensky & Barolet, 1990; Kang-Yum & Oransky, 1992; Bensky & Gamble, 1993; Kew et al, 1993;
24
25 Delves & Frost, 1995; Ravinarayan & Skandhan, 1995; Ministry of Health, 2000; Aziz et al., 2002;
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27 Ministry of Health, 2003; Mino & Yamada, 2005; Kumar et al., 2006; Sallon et al., 2006; Cooper et
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29 al., 2007; Himalaya, 2008). From the selected safety limit we calculated a tolerable weekly intake
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31 (TWI) limit for a 60 kg adult. For mercury we selected the TDI for inorganic mercury of 2 µg/kg
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33 bw/day set independently by the Dutch National Institute for Public Health and the Environment
34
35 (RIVM) and the International Program on Chemical Safety (IPCS)(Baars et al., 2001; IPCS, 2003).
36
37 This TDI is equivalent to a TWI limit of 0.84 mg per week for a 60 kg adult (Table 5). For arsenic we
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39 selected the TDI for inorganic arsenic set by RIVM of 1.0 µg/kg bw/day, equivalent to a TWI limit of
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41 0.42 mg per week for a 60 kg adult (Table 5)(Baars et al., 2001). For lead we selected the provisional
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43 tolerable weekly intake (PTWI) limit for lead from all sources of 25 µg/kg bw/wk established by the
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45 Joint FAO/WHO Expert Committee on Food Additives (JECFA), equivalent to a TWI limit of 1.5 mg
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47 per week for a 60 kg adult (Table 5)(JECFA, 1993; JECFA, 2000).
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54 In agreement with European Regulation (EC) No. 333/2007 we established for enforcement
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56 purposes for mercury, arsenic or lead each, the estimated weekly intake level at which the TWI limit is
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58 exceeded beyond reasonable doubt (European Commission, 2007). We derived these VWA action
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60 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

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3 a THP, a VWA action limit of 1.85 mg per week was derived. The VWA action limit for the estimated
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5 weekly intake of mercury was 1.31 mg per week and for arsenic the VWA action limit was a
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7 maximum estimated weekly intake of 0.510 mg per week. Recently the European Commission
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9 established for food supplements maximum product levels of 0.10 mg/kg for mercury and 3.0 mg/kg
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11 for lead, which will enter into force on the 1st of July 2009 (European Commission, 2008). No limit
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13 has yet been proposed for arsenic in food supplements. We also applied these EU maximum levels to
14
15 our data to estimate the effect of this new legislation on the availability of Asian THPs with mercury
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17 or lead on the Dutch market. Furthermore, we applied safety limits used in several pertinent studies on
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19 mercury, arsenic or lead in Asian THPs to our data in order to explore how the selection of other
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21 relevant limits would have affected the outcome of the study.
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28 Results

29 *Mercury, arsenic or lead contents of THPs*

30
31 In total 186 (64%) of 292 THPs used in Ayurveda, TCM and TTM contained arsenic, mercury or lead.
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33 Figure 1 shows for lead, mercury and arsenic separately, how the THPs are distributed over increasing
34
35 concentration ranges of these elements. The labeling of less than 20% of the THPs did contain
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37 indications that matched an entry of tables 1, 2 or 3, which would suggest the presence of ingredients
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39 with mercury, arsenic or lead levels. The remaining THPs were sampled according the general criteria
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41 of the defined sampling protocol to test the presence of mercury, arsenic or lead in Asian THPs
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43 prevalent on the Dutch market.
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49 Lead was present in 123 (42%) THPs and levels ranged from 0.5 to a maximum of 60,000
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51 mg/kg that was found in the Ayurvedic THP vasant yog. The average lead level in the positive samples
52
53 was 1,000 mg/kg; the median level was 13 mg/kg and the 95th percentile 573 mg/kg. Mercury was
54
55 found in 131 (45%) THPs in levels from 0.2 up to 171,000 mg/kg and the highest concentration was
56
57 found in the Ayurvedic THP yogendra ras. The average mercury level in the positive samples was
58
59 11,800 mg/kg, the median level was 50 mg/kg and the 95th percentile was 86,000 mg/kg. In 105 (36
60
%) of the 292 collected THPs arsenic was present in levels ranging from 0.2 up to 89,800 mg/kg, the

1
2
3 latter in the Ayurvedic THP swashanti yog. The average arsenic level in the positive samples was
4
5 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
6
7 few cases low levels of cadmium were found but the associated estimated intakes were not above
8
9 international safety limits (data not shown). Table 6 shows for lead, arsenic and mercury separately the
10
11 number of Ayurvedic, Chinese and Tibetan THPs in which these elements were detected above the
12
13 LOQ.
14

15 16 17 18 *Estimated weekly metal or metalloid intakes in relation to the selected safety limits*

19
20 In total 64 (22%) of 292 THPs were likely to result in weekly intakes of lead, arsenic or mercury
21
22 separately or in combination, above the selected TWI limits when used according to recommendations.
23
24 Levels of these elements in 59 of these 64 THPs would result in intakes that also exceeded the VWA
25
26 action limits; this signified that in total for 59 (20%) of the 292 THPs the estimated intakes of lead,
27
28 arsenic or mercury would exceed the selected TWI limits beyond reasonable doubt (Table 7). In total
29
30 25 THPs from table 7 carried indications that according to table 1, 2 and 3 suggested that ingredients
31
32 high in mercury, arsenic or lead, could be present. Use according recommendations of the Ayurvedic
33
34 THPs 'raja parvatini', 'vasant yog' and 'nature slim' would result in daily doses of lead, mercury and
35
36 arsenic above all 3 VWA action limits simultaneously.
37
38

39
40 Figure 2 shows for lead, mercury and arsenic respectively the distribution of THPs over
41
42 increasing ranges of weekly intake estimates in relation to the individual TWI limits for these
43
44 elements. The median intake of lead with THPs positive for this metal was 0.11 mg/wk, the median
45
46 intake of mercury with THPs mercury containing this metal was 0.52 mg/wk and the median arsenic
47
48 intake with THPs positive for this metalloid was 0.08 mg/wk. The lead intake estimates at proposed
49
50 dose levels for 10 THPs exceeded the TWI limit of 1.5 mg lead per week (range 1.6 - 192 mg/wk)
51
52 (Figure 2) and the lead intake estimates for 8 of these also exceeded the VWA action limit of 1.85
53
54 mg/wk. Of these 10 THPs, 8 THPs would at their proposed dose levels also result in intakes above
55
56 TWI limits for arsenic or mercury or both as well. The estimated mercury intake at the proposed dose
57
58 level of 55 THPs would be above the TWI limit of 0.84 mg inorganic mercury per week (range 0.92 -
59
60 1747 mg/wk) (Figure 2) and mercury intake estimates of 50 of these were also above the VWA action

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2
3 limit of 1.31 mg/wk. Of 26 of these 55 THPs, the intake of arsenic or lead resulting from their
4
5 proposed dose levels, would also be in excess of the TWI limits for one or both of these two elements.
6

7
8 We found 29 THPs where the proposed dose levels would result in arsenic intakes above the TWI
9
10 limit for arsenic (range 0.44 - 427 mg/wk) (Figure 2) and the proposed dose levels of 26 of these
11
12 5 would result in intakes above the VWA action limit for arsenic of 0.510 mg/wk. Additionally, the
13
14 proposed dose levels of 24 of these 29 THPs would also give rise to mercury or lead intakes in excess
15
16 of the TWI limits selected for these metals.
17

18
19 Table 8 shows for lead, mercury and arsenic separately, the number of Ayurvedic, Chinese THPs and
20
21 Tibetan THPs for which use at their proposed dose levels would result in intakes above TWI limits for
22
23 10 each of these elements.
24

25
26 In addition to the TWI limits applied above, we also compared our estimated intake data to
27
28 other relevant safety limits for mercury, arsenic and lead as well as to the maximum levels for lead and
29
30 mercury in food supplements recently established by the European Commission (European
31
32 Commission, 2008). Table 9 shows the number of THPs where use according to recommendations
33
34 15 would result in intakes of mercury, arsenic and lead above these other safety limits. When the newly
35
36 defined European maximum levels for lead and mercury were applied, the highest number of
37
38 exceedances was seen: 101 (82%) of 123 of THPs positive for lead and 130 (99%) of 131 of the
39
40 products containing mercury were above these limits (Table 9).
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42
43
44

45 20 **Discussion**

46
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48 Mercury, lead and arsenic were detected in 186 (64%) of 292 THPs used in Ayurveda, TCM and TTM
49
50 sampled in the Netherlands. Use at the proposed dose levels of 59 (20%) of these 292 THPs would
51
52 result in estimated mercury, arsenic and lead intakes significantly above established safety limits.
53

54
55 Furthermore, 82% of the THPs with lead and 99% of the THPs containing mercury exceeded the
56
57 25 recently established European maximum product levels for food supplements (Table 9)(European
58
59 Commission, 2008). Our results are in good agreement with several studies on mercury, arsenic and
60
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

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3 by 20-fold to up to 2750-fold (Cooper et al., 2007). In our study 5 (12%) of 42 Chinese THPs could
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5 result in estimated mercury, arsenic or lead intakes exceeding safety limits in a range of 1.1-fold to
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7 more than 2000-fold (Tables 7 and 8).
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10 In order to identify THPs possibly high in mercury, arsenic or lead beforehand, we screened
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12 5 the labeling for traditional names for Asian THPs or traditional names for ingredients as listed in tables
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14 1-3, which can contain arsenic, lead or mercury. Of the 59 THPs in our study that would result in
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16 mercury, arsenic or lead intakes significantly above TWI limits, the labeling of 25 (42%) carried
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18 indications from table 1-3, which could suggest high levels of these elements (Table 7). Our sampling
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20 protocol, which includes tables 1-3, was therefore helpful in identifying products with significant
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22 10 mercury, arsenic or lead levels which carried traditional product names or ingredients on the labeling.
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24 However, it proved not to be effective in identifying high-risk THPs with incomplete ingredient lists or
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26 modern product names. Our data suggests that consumers cannot rely on the labeling for avoiding
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28 THPs with high amounts of mercury, arsenic or lead and that there is a significant risk of inadvertent
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30 exposure to these elements from Asian THPs.
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34 15 In order to estimate the risks associated with exposure to mercury, arsenic or lead from Asian
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36 THPs appropriate safety limits have to be selected. Table 9 shows that the selection of a safety limit
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38 considerably influences the outcome of the study which should be considered when interpreting results
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40 of studies into mercury, arsenic or lead in THPs. It is pertinent that the differences in toxicity of the
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42 various species of an element are taken into account (WHO, 2006). Reports on the speciation of
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44 20 mercury, arsenic or lead in Asian THPs are scarce. Establishing the speciation of elements is less
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46 straightforward for Ayurvedic THPs than for Chinese THPs because Ayurvedic THPs are subjected to
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48 more rigorous processing steps that include heat treatments. The ultimate mercury, arsenic or lead
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50 species in Ayurvedic THPs are therefore more likely to differ from the initial species in the starting
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52 materials.
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55 25 Mercury from Ayurvedic THPs requires special consideration. Purified mercury (parada) is
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57 used as the starting material for most mercury containing Ayurvedic THPs. Elemental mercury shows
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59 a low oral toxicity when compared to organic and inorganic mercury compounds (ICPS, 2003;
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Baldwin & Marshal, 1999; Neustadt & Piczenik, 2007). To test if Ayurvedic THPs contained any

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3 residual elemental mercury we performed a pilot study on 23 Ayurvedic THPs in which we had shown
4 mercury to be present. No elemental mercury was detected in these products (data not shown), which
5 indicates that all mercury detected relates to either inorganic or organic mercury. For the preparation
6 of Ayurvedic THPs, mercury is mixed with sulfur until kajjali (black mercuric sulfide, HgS) is formed
7
8 (Dash, 1986; Ministry of Health, 2000; Ministry of Health, 2003; Himalaya, 2008). Mercury reacts
9 with sulfur, which forms HgS (Fuhrmann et al., 2002; Baughman, 2006). The presence of HgS in
10 Ayurvedic THPs was analytically confirmed for the important Ayurvedic mercury preparation
11 Makaradhwaja (Kumar et al., 2006), which is based on kajjali (Dash, 1986). The preparation was
12 shown to contain 85.3% mercury and 14.2% sulfur matching the stoichiometry of HgS (Kumar et al.,
13 2006). Use of mercuric sulfide in an Indian ethnic remedy in a daily dose of 180-252 mg during 4
14 weeks resulted in adverse effects consistent with a mercury poisoning (Kew et al, 1993). Inorganic
15 mercury poisonings from oral use of Chinese THPs with calomel (mercurous chloride, Hg₂Cl₂) (Kang-
16 Yum & Oransky, 1992) and cinnabar (used long-term) have been recorded (Liu et al., 2008a). Studies
17 on rats and guinea pigs have shown that mercuric sulfide and its natural form cinnabar are bioavailable
18 and neurotoxic (Chuu et al., 2001; Young et al., 2002; Chuu et al., 2007). Because methylmercury is
19 primarily formed through methylation by microorganisms (Satoh, 2000; ICPS, 2003) and because
20 methylmercury is not used in traditional medicines (Liu et al., 2008a) we considered the presence of
21 this compound in toxicological relevant quantities to be unlikely. The JECFA PTWI for total mercury
22 used by Cooper et al. (2007) is mainly applicable to diets with high consumption of fish with high
23 levels in methylmercury (JECFA, 1989b) and does not necessarily apply to foods high in inorganic
24 mercury (JECFA, 1972). Therefore a TDI for inorganic mercury (Baars et al., 2001; IPCS, 2003) was
25 selected for the risk assessment of mercury from Asian THPs. Although this TDI is based on a
26 NOAEL for inorganic mercuric chloride it also applies to other inorganic mercury compounds such as
27 mercuric sulfide (Baars et al., 2001; IPCS, 2003).

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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, As₄S₄) and orpiment (talaka, As₂S₃) (Ministry of Health, 2000;
Ministry of Health, 2003). From talaka a bhasma is made. Talaka bhasma was reported to contain

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3 As₂S₃ (Kumar et al., 2006). Furthermore arsenic trioxide (As₂O₃) was found in two kushtas from India
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5 and Pakistan (Aslam et al., 1979). Arsenic trioxide is significantly more toxic than orpiment and
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7 realgar (Liu et al., 2008). Inorganic arsenic compounds are more toxic than several organic arsenic
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9 compounds, notably those compounds (eg. arsenobetaine) which can be found in seafood in
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11 considerable quantities and which are not of major toxicological concern (IPCS, 2001). A case of
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13 arsenic poisoning involving Indian preparations has been reported in Italy (Muzi et al., 2001) and in
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15 the UK where use of Indian preparations resulting in intakes of up to 210 mg As₂O₃ per day for more
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17 than 4 months, caused symptoms consistent with inorganic arsenic poisoning (Kew et al., 1993). An
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19 Indian case of arsenic poisoning showed keratosis after 6 months of use of several Ayurvedic
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21 preparations with significant arsenic levels and after 18 months of use non-cirrhotic portal
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23 hypertension was diagnosed (Khandpur et al., 2008). Several chronic arsenic poisonings with Chinese
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25 THPs have been reported which resulted in cutaneous manifestations such as malignancies and kerotic
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27 plaques (Chan, 1994; Wong et al., 1998; Lee et al., 2004; Hanjani et al., 2007). We selected a TDI for
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29 inorganic arsenic set by RIVM for the risk assessment of arsenic from Asian THPs. The TDI is based
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31 on the JECFA PTWI for inorganic arsenic (JECFA, 1989a) to which an extra uncertainty factor of 2
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33 was applied for observation errors in epidemiological studies (Baars et al., 2001).
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38 Lead in Ayurvedic and Chinese THPs is mostly found in inorganic form. Reported forms are
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40 PbS and PbO, which can cause intoxications (Ravinarayan & Skandhan, 1995; Delves & Frost, 1995;
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42 ICPS, 1995; Healy & Aslam, 1986). A large number of lead poisonings with Ayurvedic THPs has
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44 been reported (Dunbabin et al., 1992; Kew et al, 1993; Sheerin et al., 1994; Keen, 1994; Bayly et al.,
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46 1995; Prpic-Maijc et al., 1996; van Vonderen et al., 2000; Anderson et al., 2001; Tait et al., 2002;
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48 CDC, 2004; Schilling et al., 2004; Kanen & Perenboom, 2005; van Schalkwyk et al., 2006). These
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50 reports contradict the claim that lead in Ayurvedic THPs is detoxified. A case of lead poisoning with a
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52 Chinese THP has been recorded in Hong Kong (Auyeung et al., 2002). The US Environmental
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54 Protection Agency (US EPA) did not establish an oral reference dose (RfD) for lead nor was the
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56 Agency for Toxic Substances and Disease Registry (ATSDR) able to derive a minimal risk level
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58 (MRL) for lead, because both agencies could not define a clear threshold for some of the health effects
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60 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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8 Figure 1. Concentrations of lead, mercury and arsenic in THPs. n.d: not detected
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12 5 Figure 2. Estimated weekly intake of lead, mercury and arsenic resulting from intake of THPs at their
13 proposed use levels. 'TWI' refers to the tolerable weekly intake limit for each element; for lead the
14 TWI is 1.5 mg/wk, for mercury 0.84 mg/wk and for arsenic 0.42 mg/wk. n.d: not detected
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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.

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Element	Pharmaceutical or traditional names of preparation	Synonyms and related preparations or compounds
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Lead	lithargyrum (lead monoxide)	A: girisindura, litharge, mrddara srnga, mrddarasrnga, muddarasankha, sindura C: mi tuo seng
	A: naga bhasma	A: ahi, bhujagalauha, 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, hingulothaparada, 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
	hydrargyri oxydum rubrum (red mercury oxide)	
Arsenic	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

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2 C: traditional name used in TCM

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4 References: (Bensky & Gamble, 1993; Kang-Yum & Oransky, 1999; Ministry of Health, 2000; MCA, 2001;

5 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	caturbhujra 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; mahalakshmi vilas ras
makaradhvaja		hemagarbha pottali rasa			
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			
brhat purnacandra rasa	brihat purnachandra rasa	hrdanyarnava rasa	hridayarnava ras	maha vata vidhvamsana rasa	mahavatvidhvasan ras; mahavatvidhvasan rasa; mahavat vidhwans ras
brhat sarvajvarahara lauha	sarvajwarhar loha br.	icchabhedi rasa	ichhabhedi ras (jaypal yukta)		
brhat vangesvara rasa	bangeshwar ras brihat	jalodarari rasa		maha vatagajankusa a rasa	
brhat vatacintamani rasa	brihat vata chintamani; brihat vatchintamani rasa	jvaraghi gutika			
brhat vidyadharabhra rasa		jvarankusa rasa (ka)		maha yogaraja guggulu	maha yograj guggul
brhat visamajvarantaka		jvararyabhra			
lauha		kalakuta rasa		makara dhvaja	makardhwaj; makardhvaj rasa
brhatcchngarabhra rasa		kanakasundara rasa		mallasindura	mallasindur
candrakala rasa	chandrakala ras (Tamra Yukta)	kancanabhra rasa		manikya rasa	
candramrta rasa	chandramrit ras	kantavallabha rasa	khantavallabha rasa	manmathabhra rasa	
candramsu rasa		karpura rasa	karpur ras	maricadya taila	
		kasisadi ghrta		mrtyunjaya rasa	mrtyunjai ras
		kasturi bhairava rasa	kastoori bhairav ras	muktapancamrta rasa	mukta panchamrit ras; moti

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2		yukt	samirannaga rasa	samirannag rasa	tamra parpati	
3	naga bhasma	nag bhasma	sankha vati	shankhavati; shankh vati	tarakesvara rasa	
4	naraca rasa		saubhagya vati	saubhagya bati	tarunarka rasa	
5	navaratnarajamrganka rasa		siddhapranes vara rasa	siddhapraneshwar rasa	tribhuvanakirti rasa	tribhuvankirti
6	nidrodaya rasa		sirah suladi vajra rasa	shirahsuladrivajara ras	trivanga bhasma	tribanga bhasma
7	nityananda rasa		smrti sagara rasa	smritisagar ras; smriti sagar rasa	trivikrama rasa	
8	nrpativallabha rasa	nripatiballabha ras			unmadagajakesari rasa	
9	pancamrta lauha guggulu		sri jayamangala rasa		vajrakapata rasa	
10	pancamrta parpati	panchmrita parpati	sri ramabana rasa		vanga bhasma	
11	pancanana rasa		srinrpativallabha rasa		varisosana rasa	
12	piyusavalli rasa	piyushvali ras	srngarabhra rasa	shringarabhra ras	varja bhasma	
13	prabhakara rasa		sucikabharana rasa		vasanta malati rasa	
14	pradarantaka lauha	pradarantak lauh	sukramatrka vati	shukramatrika vati	vasanta tilaka rasa	
15	pradarantaka rasa	pradarantak rasa	sulavajrini vatika	shoolvarjini vati	vasantakusumakara rasa	vasant kusumakar rasa
16	pratapalankesvara rasa	prataplankeshwar	sutasekhara rasa	soothashekara; sutshekhar rasa; sutsjekhar rasa	vata gajankusa rasa	vatagajankush ras; vatgajankush rasa
17	purnacandra rasa	purnachandra ras		sutikabharan ras		
18	puspadhanva rasa	pushpadhanwa	sutikabharana rasa		vatagnikumara rasa	
19	putapakva visama jvarantaka lauha		svacchanda bhairava rasa		vatakulantaka rasa	vatkulantak ras; vatakulantak ras
20	rajamrganka rasa		svalpanayika curna			
21	rajata bhasma		svarna bhasma	swarna bhasma	vataraktantaka rasa	
22	rasa parpati	ras parpati	svarna parpati	swarna parpati	vatari rasa	vatari ras
23	rasakarpura		svarnabhupati rasa		vatavidhavamsana rasa	
24	rasamanikya	rasa manikya	svarnasindura		vidanga lauha	
25	rasapuspa		svarnavanga		yakrdari lauha	
26	rasaraja rasa	ras raj ras; rasraj rasa	svasa kasa cintamani rasa	shawsa kasa chintamani; swasakas chintamani rasa	yakrtplihari lauha	yakritplihari loha
27	rasasindura	rasa sindur	svasakuthara rasa	swas kuthar ras; swasa kuthara ras; shwas kuthar rasa	yogendra rasa	
28	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 Radix</i>)
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 Yinao Pian	Cinnabar	Niu Huang Jiedu Pian	Realgar	Qing Xin Wan**	
Chunyang Zhengqi Wan	Cinnabar, Realgar (+ <i>Aristolochia Radix</i>)	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 Night Sight Pills ^{SS}	high mercury content reported ^{SS}	Peaceful**	Cinnabar	Xiao'er Jindan Pian	Cinnabar (+ <i>Aristolochia manshuriensis</i>)
Ding Xian Wan*	Cinnabar	Pinggan Shuluo Wan	Cinnabar	Xiao'er Jingfeng San	Cinnabar, Realgar
Ershiwuwei Shanhu Wan	Cinnabar	Po Lung Yuen Med. Pills **	Cinnabar	Xiaoerqifengsan	Cinnabar
Ershiwuwei Songshi Wan	Cinnabar	Qianjinsan ^s	Cinnabar	Xiao'er Qingre Pian	Cinnabar, Realgar
Feierwanyaopian ^s		Qi Li San*/**	Cinnabar	Xiaoerqiyingwan ^s	Cinnabar (arsenic also detected ^s)
Geng Yi Wan*	Cinnabar	Qizhen Wan	Cinnabar, Realgar	Xiao'er Zhibao Wan	Cinnabar, Realgar
Hongling San	Cinnabar, Realgar	Renqing Changjue	Cinnabar	Xi Gua Shuang (Watermelon frost)	Cinnabar
Hua Chong Wan	Red lead oxide	Renqing Mangjue	Cinnabar	Yatong Yili Wan	Cinnabar, Realgar
Hui Chun Dan*	Cinnabar	San Li Hui Chun Dan**	Cinnabar	Yinianjin	Cinnabar
Hu Po Bao Long Wan (Po Lung Yuen Med. Pills) **	Cinnabar	Shayao	Cinnabar, Realgar		
Jian Nao Wan (healthy brain pills)**	Cinnabar	She Dan Chen Pi San**	Cinnabar		
		Sheng Tie Luo Yin			

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2	Yingerbaofeining ^s	Cinnabar
3	Yingerle ^s	Cinnabar
4	Yixian Wan	Cinnabar, Realgar
5	Yi Yuan San*	Cinnabar
6	Zaizao Wan	Cinnabar
7	Zhi Bao Dan	Cinnabar, Realgar
8	Zhou Che Wang*	Calomel
9	Zhuhuang Chuihou San	Realgar
10	Zhu Sha An Shen Wan*/** (Cinnabar sedative pill)	Cinnabar
11	Zijin Ding/ Zi Jin Ding**	Cinnabar, Realgar
12	Zixue	Cinnabar
13	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

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 (mg/kg)	LOQ (mg/kg)	Range of application (mg/kg)	Accuracy ¹ (%)	RSD _r ² (%)	Expanded Measurement 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 <u>element</u> 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.

Asian THP	Type of Asian THP*	Arsenic	Mercury	Lead
		mg/wk		
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	<i>0.44</i>	430	1.3
Ere Forte	A	n.d.	12	0.34
Femi-Smilin	A	7.5	0.73	0.33
Gandhadi Yog	A	n.d.	11	n.d.
Ghandramsu 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	<i>0.47</i>	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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2	Maha Ras Guggul	A	1.0	<i>1.2</i>	0.03
3	Mahabatbiddhonsan Ras	A	0.08	69	78
4	Makar Wazra	A	5.0	903	n.d.
5	Mutik-25	T	0.53	146	n.d.
6	Natureslim	A	79	111	192
7	Pesin	A	0.9	923	0.07
8	Raja Parvartini	A	2.2	7.2	5.4
9	Ras Yog	A	0.04	92	n.d.
10	Ru Pi Xiao Pian	C	1.1	n.d.	n.d.
11	Sanjiwani	A	427	n.d.	n.d.
12	Shatavari	A	1.3	2.4	0.14
13	Shingorabrak	A	n.d.	162	n.d.
14	Shringrabhra	A	0.8	20	0.12
15	Shringrabhra	A	n.d.	26	1.2
16	Sirshool Vajraras	A	0.05	299	1.1
17	Swas Kuthar Ras	A	66	65	0.11
18	Swashanti Yog	A	200	118	n.d.
19	Sworna Yog	A	1.5	70	n.d.
20	Tianwang Buxin Wan**	C	n.d.	24	0.17
21	Triyog Misran	A	n.d.	71	n.d.
22	Ulceromed	A	0.03	22	0.10
23	Vasant Yog	A	0.60	57	105
24	Yogendra Ras	A	0.06	274	0.18
25	Yograj Guggulu	A	0.08	1.4	<i>1.6</i>
26	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

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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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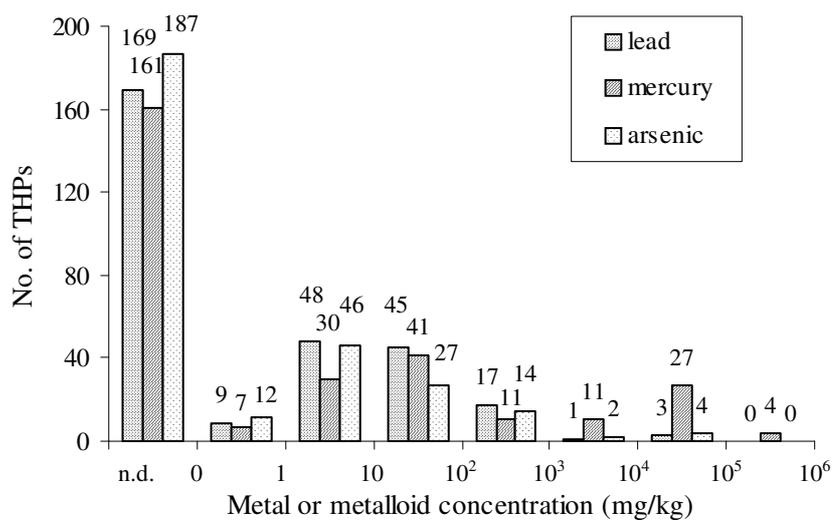
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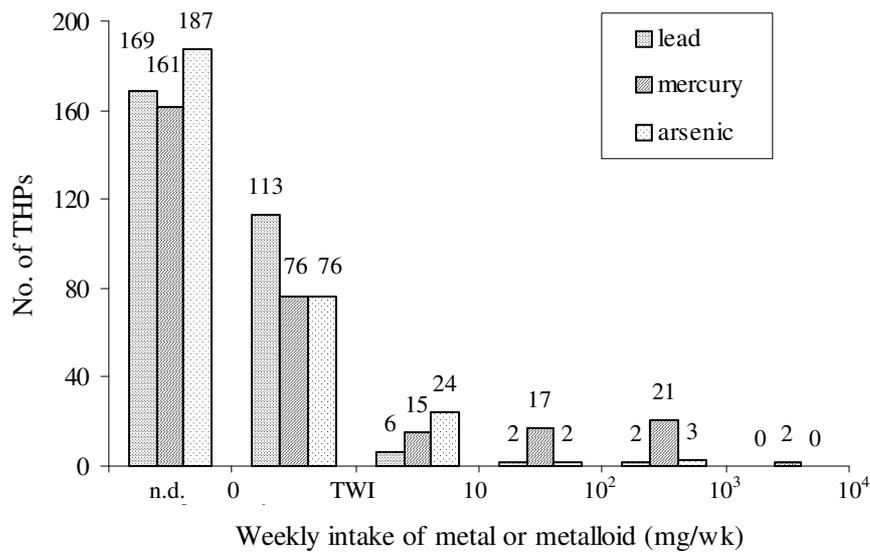
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