Heavy Metals: Analysis and Limits in Herbal Dietary Supplements

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The American Herbal Products Association

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Introduction

The term "heavy metal" is a rather poorly defined term that has come to refer to a group of elements that can be toxic when consumed by humans, including lead (Pb), mercury (Hg), cadmium (Cd), arsenic (As), and chromium (Cr).[1] There are concerns about the potential health effects of some of these elements, or specific forms of these elements, whenever they are present in products that can be ingested, such as foods or dietary supplements. Heavy metals can, in certain quantities, cause disease, be carcinogenic, have adverse reproductive effects, unfavorably impact nutrition, and displace more biologically useful metals such as calcium and zinc.[2, 3]

This document is focused on the above-listed heavy metals excluding chromium. It presents guidance developed by the American Herbal Products Association (AHPA) on maximum quantitative limits for these four elements with accompanying explanations as to how these limits were determined. It also discusses relevant regulations about the presence of these chemicals in products sold in the United States, and daily limits that have been set for these by regulatory agencies and standards-setting organizations, both within the United States and elsewhere. In addition, it reviews available analytical methods for measuring heavy metals, and provides guidance on how to determine which analytical methods are most suitable for dietary supplements and on how to choose a contract lab that can properly conduct heavy metal testing.

Regulatory background: U.S. and California

Under current good manufacturing practice (cGMP) for dietary supplements, manufacturers of supplements that are sold in the United States are required to "establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement."[4] When this rule was published by FDA in June 2007, the

[1] These substances might correctly be called toxic elements or toxic metals since they are not all heavy metals or even metals. See, for example, Duffus JH, "Heavy metals" a meaningless term? (IUPAC Technical Report) *Pure Appl. Chem.* 2002; 74(5):793-807; or Duffus JH, Toxicology of metals--science confused by poor use of terminology. *Arch Environ Health*. May 2003; 58(5):263-5; discussion 265-6. The more common nomenclature is nevertheless used throughout this document.

[2] Graeme KA and Pollack CV Jr. Heavy metal toxicity, Part I: arsenic and mercury. *J Emerg Med* 1998; 16(1):45-56.

[3] Graeme KA and Pollack CV Jr. Heavy metal toxicity, Part II: lead and metal fume fever. *J Emerg Med* 1998; 16(2):171-7.

[4] Title 21 *Code of Federal Regulations* § 111.70(b)(3), or 21 CFR 111.70(b)(3).

agency commented that "not all ingredients or dietary supplements are subject to the same types of contamination," and that it "would not be practicable or necessary to require testing for all possible contaminants for every dietary supplement, or for every component used to manufacture a dietary supplement."[5] FDA also noted that "the manufacturer has the responsibility to determine what types of contamination are likely or certain to contaminate a given product and to determine what types of tests to conduct and when to test for such contamination." [6] The agency also acknowledged, "we would not expect you to set limits for every potential contaminant or for every naturally occurring constituent of a botanical," and that FDA does not "have a 'zero tolerance' for… unavoidable contaminants," such as mycotoxins "that are found in the food supply."[7]

Thus, the federal cGMP rule does not provide a specific list of heavy metal contaminants that could potentially adulterate a dietary supplement. Instead, manufacturers determine what, if any, heavy metal specifications are appropriate under cGMP for their ingredients and finished products, and what heavy metal tests are needed, whether to meet established specifications or for other purposes. In addition, any self-imposed heavy metal cGMP specification needs to be met by the manufacturer in order to comply with the federal cGMP rule.

As noted above, this document addresses just arsenic, cadmium, lead, and mercury, and it is these four heavy metals that are most commonly the subject of attention in manufacturing dietary supplements. This does not imply that all herbal ingredients or supplements need to be tested for any one of these four elements, or that cGMP specifications for these are applicable to every herbal ingredient or supplement. Similarly, there are other heavy metals not addressed here for which testing or specifications may be appropriate for some supplements and ingredients.

In contrast to the absence of any specific federal cGMP requirement for quantitative limits on heavy metals in dietary supplements, the law commonly known as Proposition 65 (The Safe Drinking Water and Toxic Enforcement Act of 1986) in the State of California affects all products sold in the state. The law maintains mechanisms for listing chemicals that are "known to the state" to cause cancer or reproductive harm, and requires any product that exposes a consumer to any such chemical to provide a "clear and reasonable warning" unless the amount present is

[5] 72 FR 34837.

[6] Ibid.

[7] 72 FR 34840.

below established "safe harbor" limits, if such have been issued. Listed chemicals include arsenic (inorganic forms); cadmium; lead; and mercury and methylmercury.[8]

There have been numerous complaints filed against marketers of herbal dietary supplements, starting in early 2001, for failure to provide warnings on products alleged to have contained amounts of arsenic, cadmium, lead and/or mercury above the safe harbors established for these heavy metals. Settlement of these complaints have not been consistent, but have consisted of one or more of several elements, including restated requirements to place warnings on products, agreements to allow additional levels of the identified heavy metals, and financial penalties as high as $400,000.[9]

Sources and forms of heavy metal contamination

Heavy metals are naturally-occurring components of the earth's crust that are, as a rule, neither created nor destroyed, but are simply redistributed. Distribution of heavy metals is not uniform, such that some soils may contain higher amounts of any of these chemicals, either due to natural processes or to pollution factors wherein heavy metals have been disbursed into the environment through human activities, such as mining, power generation, manufacturing, and the former use of leaded gasoline.

Each of the heavy metals can be absorbed into many plants as they grow. Some plants have been reported to accumulate specific metals, such as is the case with cadmium and some genotypes of durum wheat (*Triticum turgidum* var. *duram*)[10] or St. John's wort (*Hypericum perforatum*),[11] and arsenic in numerous seaweed species.[12] In addition, airborne heavy metals may be sources of foliar contamination, at least for lead[13] and cadmium.[14]

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[8] "Chromium (hexavalent compounds)" is also listed by California as a carcinogen. AHPA is not aware of any reports of the presence of hexavalent chromium in any dietary supplement or ingredient.

[9] Additional information on Proposition 65 and heavy metals in herbal products is available in a document issued by AHPA in 2008 titled: Background on California Proposition 65 – Issues related to heavy metals and herbal products. Contact the AHPA office for availability.

[10] Harris NS and Taylor GJ (in prep). Cadmium uptake and partitioning in durum wheat during grain filling.

[11] Schneider M and Marquard R. Investigations on the uptake of cadmium in *Hypericum perforatum* L. (St. John's wort). *Acta Hort* (ISHS) 1996; 426:435-442.

[12] Rose M *et al.* Arsenic in seaweeds – forms, concentration and dietary exposure. *Food and Chemical Toxicology* 2007; 45:1263-7.

[13] Anon. 2001. Chapter 6.7: Lead, electronic version (http://www.euro.who.int/document/aiq/6_7lead.pdf), page 3. WHO Regional Office for Europe: Copenhagen, Denmark. Accessed on December 23, 2008.

Thus, manufacturers of dietary supplements may encounter some level of the heavy metals arsenic, cadmium, lead and mercury in their ingredients. Other potential sources of such contamination can be a manufacturer's water supply or the use of non-food grade equipment.

Attention must also be given to the specific form of some heavy metals since health risks are sometimes associated with, or heightened for one form more than others. Each of these can be found in an elemental state or combined with other elements. It is well established, for example, that the inorganic form of arsenic, i.e., arsenic bound with oxygen, chlorine, or sulfur, presents a significantly greater health risk than organic forms bound with carbon and hydrogen.[15] Similarly, because methylmercury is readily absorbed from the gastrointestinal tract, it is that organic form of mercury for which health concerns are most acute.[16] As will be discussed below, limits on consumption of these two heavy metals are sometimes specific to the form of inorganic arsenic and methylmercury, respectively.

Currently established quantitative limits for heavy metals

As companies that manufacture dietary supplements evaluate appropriate specifications for heavy metal levels in their products, they may review toxicity information developed by various U.S. agencies. As is shown below, however, they will find very little in the way of consistent guidance from federal health agencies on specific health-based tolerances for heavy metals in foods, including dietary supplements.

An FDA regulation on bottled water limits the allowable levels of numerous chemical contaminants, including arsenic, cadmium, lead and mercury.[17] The Environmental Protection Agency (EPA), in its National Primary Drinking Water Regulations, similarly regulates with maximum contaminant levels (MCLs) of these

[14] Anon. 2001. Chapter 6.3: Cadmium, electronic version (http://www.euro.who.int/document/aiq/6_3cadmium.pdf), page 3. WHO Regional Office for Europe: Copenhagen, Denmark. Accessed on December 23, 2008.

[15] U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Arsenic. August 2007. http://www.atsdr.cdc.gov/toxprofiles/tp2.pdf accessed on December 30, 2008.

[16] U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Mercury. March 1999. http://www.atsdr.cdc.gov/toxprofiles/tp46.pdf accessed on December 30, 2008.

[17] 21 CFR 165.110.

four heavy metals and other contaminants in "community water systems and non-transient, non-community water systems."[18]

FDA did publish, in 1993, guidance documents for some heavy metals that can be found in seafood, wherein the agency identified a "tolerable daily intake" for inorganic arsenic of 130 µg and for cadmium of 55 µg, and a "provisional tolerable total intake level" for lead of 75 µg per day (all limits specified or assumed to be for adults). But the FDA website that houses these documents currently states that they "represented current agency thinking in regards to the available science at the time they were issued," and that they "no longer represent the current state of science and are presented here for the historical record only."[19]

In the interim, in March 2004 FDA and EPA issued a joint advisory on mercury in seafood to women who are pregnant or might become pregnant, and to nursing mothers and young children.[20] These agencies advised these populations to avoid certain types of fish that are known to be high in mercury. And in November 2006, FDA issued guidance for industry on the issue of lead in candy that is likely to be eaten by children, in which it recommended "that lead levels in candy products likely to be consumed frequently by small children not exceed 0.1 ppm."[21]

Heavy metal limits have also been established by FDA for several food additives identified in 21 CFR 184. Limits are set for each of these heavy metals in bakers yeast extract, and this is the only such example for cadmium. There are four additives with a limit of 3 parts per million (ppm) arsenic (aconitic acid; gum ghatti; licorice and licorice derivatives; and rapeseed oil) and two others with lower limits (partially-hydrogenated and hydrogenated menhaden oils at 0.1 ppm; nisin preparations at 1 ppm). Mercury must not exceed 0.5 ppm in menhaden oil, whether or not hydrogenated. In addition to these, there are six food additives with prescribed lead limits (enzyme-modified lecithin at 1 ppm; gum ghatti at 10 ppm; menhaden oil, whether or not hydrogenated, at 0.1 ppm; nisin preparations at 2 ppm; and sheanut

[18] 40 CFR 141.62 for arsenic, cadmium, and mercury; 40 CFR 141.80 for lead.

[19] FDA Center for Food Safety and Applied Nutrition. Guidance documents for trace elements in seafood. 1993. http://www.cfsan.fda.gov/~frf/guid-sf.html accessed on December 23, 2008.

[20] U.S. Department of Health and Human Services and U.S. EPA. What you need to know about mercury in fish and shellfish. 2004. http://www.cfsan.fda.gov/~dms/admehg3.html accessed on December 23, 2008.

[21] FDA Center for Food Safety and Applied Nutrition. Guidance for industry – Lead in candy likely to be consumed frequently by children: Recommended maximum level and enforcement policy. 2006. http://vm.cfsan.fda.gov/~dms/pbguid3.html accessed on December 23, 2008.

oil at 0.1 ppm), and six others with a limit of total heavy metal impurity of 10 ppm, including cocoa butter substitute, glycerol palmitosterate, and four forms of whey.

But aside from the limited examples identified above, FDA has not addressed the issue of heavy metals in foods, and has not instituted any regulation or provided contemporary recommendations for heavy metal tolerances for conventional foods generally, or for dietary supplements.[22] FDA does however recognize the current *Food Chemicals Codex* (*FCC*) and the *United States Pharmacopeia-National Formulary* (*USP-NF*) national standards as official sources for the purpose of specifying contamination limits in dietary supplements even though such limits may be on a concentration basis.

In addition to its occasional FDA-cooperative communications on heavy metal risks in some foods, EPA, with its broad environmental mandate, created the Integrated Risk Information System (IRIS) database in 1985. EPA maintains IRIS as "an electronic database containing information on human health effects that may result from exposure to various substances in the environment." The many substances listed in IRIS include each of the heavy metals discussed here, and EPA has established a "reference dose" (RfD) for inorganic arsenic, cadmium, and methylmercury. The agency describes an RfD as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."[23] No RfD has been established for lead, and EPA has recorded its belief that some of the effects of lead consumption "may occur at blood lead levels so low as to be essentially without a threshold."[24]

The Agency for Toxic Substances and Disease Registry (ATSDR) (within the U.S. Department of Health and Human Services) also has developed a model for evaluating heavy metals, and has established and maintains "minimal risk levels"

[22] FDA maintains a list of "action levels for poisonous or deleterious substances in human food and animal feed" (see http://www.cfsan.fda.gov/~lrd/fdaact.html, accessed on December 23, 2008) that identifies cadmium, lead and mercury. The relevance of these, however, is quite limited. The action level for cadmium is relevant only to ceramicware and that for lead only to ceramicware and silver-plated hollowware. It is only mercury for which action can be taken on foods, but only when methylmercury is present at > 1 ppm on the edible portion of fish (including shellfish and crustaceans), and on pink wheat kernels when an average of 10 or more pink kernels are present in 500 grams.

[23] U.S. Environmental Protection Agency. Integrated Risk Information System: Arsenic, inorganic; CASRN 7440-38-2 (04/10/1998). http://www.epa.gov/ncea/iris/subst/0278.htm accessed on December 23, 2008.

[24] U.S. Environmental Protection Agency. Integrated Risk Information System: Lead and compounds (inorganic); CASRN 7439-92-1. http://www.epa.gov/ncea/iris/subst/0277.htm accessed on December 30, 2008.

(MRLs) for oral consumption of arsenic, cadmium and methylmercury.[25] ATSDR was established in 1980 when the U.S. Congress passed the "Superfund law," and its primary mission is directed toward hazardous waste sites. Nevertheless, the MRLs calculated by this agency may provide some guidance in determining reasonable specifications for foods and dietary supplements. It should be noted that ATSDR has also refrained from setting an MRL for lead "because a clear threshold for some of the more sensitive effects in humans has not been identified."[26]

A summary of the limits on heavy metals discussed above and provided by one or another U.S. federal agency is provided in Table 1a below. References for the data contained in Table 1a are the same as those identified in the footnotes for this section of this document.

[25] U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. ATSDR Minimal Risk Levels. November 2007. http://www.atsdr.cdc.gov/mrls/pdfs/mrllist_11_07.pdf accessed on December 23, 2008.

[26] U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Lead. August 2007. http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf accessed on December 23, 2008.

Table 1a. U.S. Agencies: Current quantitative heavy metal limits

	Agency / Scope	Stated Limit	Calculated Daily Limit (Adult)
Arsenic	FDA / Bottled drinking water	Allowable level = 10 µg arsenic /liter.	**20 µg** (calculated at 2 liters/day)
	EPA / Drinking water	MCL = 10 µg arsenic/liter.	**20 µg** (calculated at 2 liters/day)
	EPA / IRIS	RfD (chronic effect; noncancer) = 0.3 µg *inorganic* arsenic/kg bw.	**21 µg** (calculated at 70 kg)
	ATSDR	MRL (chronic oral consumption) = 0.3 µg *inorganic* arsenic/kg bw	**21 µg** (calculated at 70 kg)
Cadmium	FDA / Bottled drinking water	Allowable level = 5 µg cadmium /liter.	**10 µg** (calculated at 2 liters/day)
	EPA / Drinking water	MCL = 5 µg cadmium/liter.	**10 µg** (calculated at 2 liters/day)
	EPA / IRIS	RfD (chronic effect; noncancer) = 1.0 µg cadmium/kg bw.	**70 µg** (calculated at 70 kg)
	ATSDR	MRL (chronic oral consumption) = 0.2 µg cadmium/kg bw	**14 µg** (calculated at 70 kg)
Lead	FDA / Bottled drinking water	Allowable level = 5 µg lead/liter.	**10 µg** (calculated at 2 liters/day)
	EPA / Drinking water	Action level = 15 µg/liter.	**30 µg** (calculated at 2 liters/day)
Mercury	FDA / Bottled drinking water	Allowable level = 2 µg mercury/liter.	**4 µg** (calculated at 2 liters/day)
	EPA / Drinking water	MCL = 2 µg mercury/liter.	**4 µg** (calculated at 2 liters/day)
	EPA / IRIS	RfD (chronic effect; noncancer) = 0.1 µg *methylmercury*/kg bw.	**7 µg** (calculated at 70 kg)
	ATSDR	MRL (chronic oral consumption) = 0.3 µg *methylmercury*/kg bw	**21 µg** (calculated at 70 kg)

Looking beyond the United States, international organizations have also worked to develop recommendations for limits on heavy metal consumption. A joint committee on food additives convened by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations (JECFA, or the Joint Expert Committee on Food Additives) has been meeting since 1956 and has established "provisional tolerable weekly intakes" (PTWI) for each of the heavy metals that are the subject of this document. The JECFA level for methylmercury is at the high end of the range of such values set by the U.S.-based entities identified in

Table 1a, while the levels for the other three chemicals are significantly higher than the U.S. agencies' recommendations.

These JECFA levels are presented below in Table 1b.[27] Of additional interest in considering these levels is the fact that entities within the European Commission have endorsed or adopted the JECFA values for cadmium, lead and mercury, as is indicated in the notes to Table 1b.

Table 1b. JECFA (and EU as indicated) heavy metal limits

	Stated Limit (PTWI - weekly)	Calculated Daily Limit (Adult, 70 kg)	EU Status
Arsenic	15 µg *inorganic* arsenic/kg bw	**150 µg**	No information found
Cadmium	7 µg cadmium/kg bw	**70 µg**	Endorsed 6/2/1995
Lead	25 µg lead/kg bw	**250 µg**	Endorsed 6/19/1992
Mercury	1.6 µg *methylmercury*/kg bw	**16 µg**	Adopted 2/4/2004

Numerous countries and several pharmacopoeial references have published limits on allowable concentrations of heavy metals, stated in mg/kg or ppm, for finished food products and/or dietary supplement type products, or ingredients used in these products. Canada may be unique, however, in having established specific daily maximum levels stated in total amounts consumed for finished "Natural Health Products" (NHPs), that country's classification for the kinds of products sold as dietary supplements in the U.S. The obvious value of this approach is that it takes into account a product's dosage amount. The levels established by Health Canada for NHPs[28] are recorded in Table 1c.

[27] The PTWI for arsenic is recorded in WHO Food Additive Series: 24 (Cambridge University Press, 1989), as extracted at http://www.inchem.org/documents/jecfa/jecmono/v024je08.htm, while that for lead is in WHO Food Additive Series: 44 (WHO, 2000), at http://www.inchem.org/documents/jecfa/jecmono/v44jec12.htm. For cadmium and methylmercury, see WHO Food Additive Series: 52, pages 556 and 615, respectively (WHO, 2004 http://whqlibdoc.who.int/publications/2004/924166052X.pdf). All accessed on December 23, 2008.

[28] Health Canada. Natural Health Products Compliance Guide, version 2.1. January 2007.

Table 1c. Heavy metal limits for Canada's Natural Health Products

	Stated Limit	Calculated Daily Limit (Adult, 70 kg)
Arsenic	0.14 µg "arsenic and its salts and derivatives"/kg bw*	**10 µg**
Cadmium	0.09 µg cadmium/kg bw	**6 µg**
Lead	0.29 µg lead/kg bw	**20 µg**
Mercury	0.29 µg "mercury and its salts and derivatives"/kg bw	**20 µg**

* Health Canada is reportedly considering establishment of a limit of 0.03 µg *inorganic* arsenic/kg bw. See Kyeyune V and Marles R. May 20, 2008. Organic and inorganic arsenic in Natural Health Products; Issue Analysis Summary (IAS). See http://standards.nsf.org/apps/group_public/download.php/1436/4-addendum%20-%20DS-2008-2%20Arsenic%20HC%20-%20summary.pdf. Accessed on December 23, 2008.

The final government entity that sets limits for heavy metals and that must be considered in any review of existing standards is the State of California's Office of Environmental Health Hazard Assessment (OEHHA). This agency has responsibility for implementing California's Proposition 65 regulations, and regularly publishes information on "safe harbor" levels below which warning labels are not required on products that may contain one or more listed heavy metal. Table 1d presents the current levels established by OEHHA for these chemicals, with levels for carcinogens established as "no significant risk levels" (NSRLs) and those for developmental toxins as "maximum allowable dose levels" (MADLs).[29]

[29] California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Branch. Proposition 65 Safe Harbor Levels: No significant risk levels for carcinogens and maximum allowable dose levels for chemicals causing reproductive toxicity. May 2008.

Table 1d. Current "safe harbor" levels under California Proposition 65

	Carcinogen	Reproductive Toxicant
	NSRL (μg/day)	MADL (μg/day)
Arsenic [a]	10 [b]	No MADL recorded [c]
Cadmium [d]	0.05 (inh) [e]	4.1
Lead [f]	15 [g]	0.5
Mercury [h]	No NSRL recorded [i]	No MADL recorded [j]

[a] The specific chemical listed as a carcinogen is "arsenic (inorganic arsenic compounds)," while that listed as a developmental toxin is "arsenic (inorganic oxides)."

[b] Limit for inhaled arsenic is 0.06 μg/day; the level given here is the limit for exposure by other routes, e.g., ingestion, and is identified simply as "arsenic," even though the listed chemical is inorganic arsenic.

[c] "Arsenic (inorganic oxides)" is listed in OEHHA's current (May 2008) "safe harbor" publication as a "second priority" for establishment of a MADL. A "draft oral MADL" of 0.1 μg/day for "arsenic (inorganic oxides)" was identified by OEHHA in 2003.

[d] The carcinogen listing is for "cadmium and cadmium compounds," while "cadmium" is listed as a male developmental toxin.

[e] The number given here for cadmium is for inhalation; no level is given for oral consumption and cadmium is not generally considered carcinogenic by the oral route; the listing of cadmium in the Proposition 65 list does not, however, state this clearly.

[f] "Lead" is listed as a developmental toxin. "Lead and lead compounds," as well as "lead acetate," "lead phosphate" and "lead subacetate" are listed as carcinogens.

[g] This is the oral level given for lead as a carcinogen. Separate (and higher) levels are identified for lead acetate (23 μg/day), lead phosphate (58), and lead subacetate (41).

[h] The carcinogen listing is for "methylmercury compounds." Listings as developmental toxins include "mercury and mercury compounds" and "methyl mercury."

[i] "Methylmercury compounds" is recorded as a "third priority" for establishment of an NSRL as of May 2008.

[j] Both "mercury and mercury compounds" and "methyl mercury" are currently (May 2008) listed as "second priorities" for development of MADLs. A "draft MADL" of 0.3 μg/day for methyl mercury was identified by OEHHA in 1994.

Additional information relevant to the California safe harbor limits can be gleaned from several settlements that have made by companies that were the defendants in complaints that their products were alleged to contain one or more of these heavy metals. One recent such settlement[30] established a "naturally occurring" level of 2.25 μg of lead, so that the defendant will only be required to provide warnings on products with a daily level over 2.75 μg (2.25 plus the 0.5 established as the MADL for lead), so long as other criteria, including analysis of representative samples by a particular specified method (ICP-MS; see discussion below), are met.

Earlier settlements in 2005 addressed not only lead, but also arsenic, cadmium and mercury. In these the defendants again agreed to specific analytical practices, and to

[30] Superior Court of the State of California, City and County of San Francisco. *As You Sow v. Ideasphere, Inc. and Twinlab Corporation.* Order re: motion to approve Proposition 65 settlement and for entry of consent judgment. June 4, 2008.

a "naturally occurring" level of 3.5 µg of lead (so warnings are required above 4.0 µg/day), and daily "stipulated exposure levels," above which warnings are required, of 10 µg arsenic (assumed to be total arsenic) and 4.1 µg cadmium. These settlements addressed mercury as two separate forms, so that the stipulated exposure level for "mercury and mercury compounds, except inorganic mercury" was agreed to be 0.3 µg/day, while "inorganic mercury" was set at 3.0 µg/day.[31]

These settlements, though approved by the California judiciary system, must be recognized as agreements that are limited to the parties involved and so do not extend to other companies, and do not, in fact, protect the settling company from other possible plaintiffs or even the State of California itself. Nonetheless, the terms of these agreements are of interest to marketers of dietary supplements generally.

In summary, governmental bodies and other organizations in the United States, in California, and in several international venues, have provided information relevant to limits on daily consumption of arsenic, cadmium, lead and mercury.[32] Some of these have provided levels for total daily consumption from all sources, while others have focused on the intake of these heavy metals from a single source. Only Health Canada has specified limits for individual finished "natural health products," which are generally similar to products sold as dietary supplements in the United States, though the attention of California plaintiffs has had the effect of making the limits established under Proposition 65, and especially the lower MADLs, of additional relevance to daily doses of supplements sold in that state.

[31] See, for example, Superior Court of the State of California, County of San Francisco. *As You Sow v. Botanical Laboratories, Inc. et al.* Order re: motion to approve Proposition 65 settlement and for entry of consent judgment. May 23, 2005.

[32] See the appendix for additional established limits grouped by heavy metal.

Analytical methods for testing of heavy metals

There are two basic types of analytical methods for assaying heavy metals. The classical ones are colorimetric, where the concentrations of heavy metals are measured as a group of like elements. The newer instrumental methods measure individual elements.

Colorimetric methods

Colorimetric analytical methods have been in use for over 100 years[33] and are based on measuring color changes of solutions that arise from specific chemical interactions. The most familiar colorimetric test relevant to analysis of heavy metals in herbs and herbal products is described in the *USP-NF* General Chapter <231> Heavy Metals, though a recent *Pharmacopeial Forum* stimuli article suggests replacement of this general chapter with more up to date information.[34] The current test creates a chemical reaction that is compared with a standard prepared from stock lead nitrate. It relies on the ability of lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum to react with thioacetamide-glycerin base TS at a pH of 3.5 to produce a color that is then compared with the standard preparation. It can be used to demonstrate that the content of metallic impurities colored by sulfide ions under the specific test conditions do not exceed a certain limit.

In order to prepare herbal dietary supplement samples for colorimetric analysis they must undergo a chemical reaction that, depending on the method, requires a decarbonization step with concentrated nitric and sulfuric acids followed by digestion with hydrochloric acid, or digestion with concentrated nitric and sulfuric acids followed by hydrogen peroxide if needed. The advantage of this method is that it can be performed using basic glassware and normal laboratory reagents and equipment. It does not require any expensive instrumentation. The disadvantages, however, are that the detection limit for colorimetric methods is in the 10-20 ppm range where all the responding metals, including some beneficial elements such as copper, molybdenum, tin, and silver are also measured as lead equivalents. Thus, the use of this method can not ensure that heavy metal specifications established at very low levels are met. Additionally a recent Institute of Medicine workshop on USP

[33] Simoni RD, Hill RL, and Vaughn M. Analytical Biochemistry: the Work of Otto Knuf Olof Folin on Blood Analysis. *J. Biol. Chem* 2002; 277(20):19-20.

[34] http://www.usp.org/pdf/EN/USPNF/2008-04-10InorganicImpuritiesStim.pdf accessed on December 23, 2008.

heavy metals testing methodologies revealed that heavy metals are not well recovered by this method and mercury not at all.[35]

Another colorimetric test, *USP-NF* General Chapter <251> Lead, is a procedure for measuring lead by selectively extracting it from the sample. This procedure is fairly long and uses sulfuric acid, hydrogen peroxide, potassium cyanide, dithizone, and chloroform. The advantages to this method are similar to those for the heavy metal test of *USP-NF* General Chapter <231> while the disadvantages include a high detection limit, which again calls into question the usefulness of this method for meeting specifications at very low levels, and its limited specificity to lead. Cadmium, arsenic, and mercury are not detected by this method.

Instrumental methods

There are four instrumental methods routinely used to measure heavy metal levels. They are flame atomic absorption spectroscopy (FAAS), graphite furnace atomic absorbance spectroscopy (GFAAS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and inductively coupled plasma-mass spectroscopy (ICP-MS). The sample preparation for all these methods relies on digestion of the sample using concentrated nitric acid and/or hydrochloric acid, and hydrogen peroxide.

FAAS is the oldest of these techniques and relies upon the electrochemical properties of metals that allow them to absorb energy from light of specific wavelengths. More atoms of a selected element that are exposed to the correct wavelength, and absorb it, will increase the total amount of light absorbed. The relationship between the amount of light absorbed and the concentration of analytes present in known standards can be used to determine sample concentrations by measuring the amount of light that they absorb.

GFAAS is similar to FAAS, but uses a different sampling system. FAAS uses a relatively inefficient system where only a small fraction of the sample reaches the atomizing flame before quickly passing through the light path. GFAAS uses an improved sampling device that atomizes the entire sample and retains it in the light path for an extended period of time. This is done by replacing the flame used in FAAS with an electrically heated graphite tube. These changes significantly improve the detection limits of the technique.

[35] http://www.iom.edu/CMS/3788/54057.aspx accessed on December 23, 2008.

ICP-AES uses argon inductively coupled plasma maintained by the interaction of a radio frequency field and ionized argon gas to excite atoms to unstable energy configurations. The excess atomic energy is released as emitted light when the atoms return to more stable configurations. The wavelengths of the energy released are specific to the elements in the sample, and the intensity of the emission is a function of the concentration of atoms that are affected. ICP temperatures reach as high as 10,000 degrees Kelvin with samples experiencing temperatures between 5,500 and 8,000 degrees Kelvin.

ICP-MS retains the sample introduction system used in ICP-AES but the atomic ions produced by the argon plasma are directed into a mass spectrometer (MS). The MS separates the ions introduced from the ICP according to their mass-to-charge ratio. Ions of the selected mass-to-charge ratio are directed to the detector, which records the ions present. This provides identification and quantification of the elements of interest. Typically a quadrupole mass analyzer spectrometer is used due to its ease of use, robustness and speed. However, other mass analyzer systems such as ion-trap, sector field, and time of flight can be used.

A fifth instrumental method, X-Ray Fluorescence Spectrometry (XRF), is seeing some use as a screening tool due to the availability of hand-held field instruments. XRF employs x-rays to ionized elements and records the characteristic emissions of atoms as they return to more stable energy states. It is fast, relatively inexpensive, requires minimal sample preparation, can identify many elements at once, but is only moderately sensitive.

A comparison of instrumental methods

All of these instrumental methods have advantages and disadvantages including but not limited to interferences, detection limits, sample throughput, linear dynamic range, precision, ease of use, applicability, sample volume required, dissolved solids handling, unattended use, method development, initial costs, operating costs, and cost per sample. To discuss all these in depth is beyond the scope of this document; however, Table 2 below provides a tabular overview.

Table 2. Comparison of various instrumental techniques[36]

	FAAS	GFAAS	ICP-AES	ICP-MS	XRF
Detection limit	Very good for some elements	Excellent for some elements	Very good for some elements	Excellent for most elements	Very good for some elements
Analytical capability	Single element	Single element	Multi-element	Multi-element	Multi-element
Linear dynamic range	10^3	10^2	10^5	10^5	10^5
Sample through put	10 sec/element	2 min/element	5-30 elements/ min/sample	All elements 2-6 min/sample	5-15 min
Precision	0.1-1%	1-5%	0.3-2%	1-3%	1-10%
Interferences spectral	Few	Very few	Common	Few	Few
Interferences chemical	Many	Many	Very few	Some	Some
Interferences physical	Some	Very few	Some	Some	Some
Dissolved solids	Up 5 %	Up to 10%	Up to 20%	0.1-0.4%	Up to 100% solid
Applicability	>60%	>50%	>70%	>80%	>80%
Method development	Easy	Fairly easy	Fairly easy	More difficult	Fairly easy
Ease of use	Easy	Easy	Easy	Easy	Easy
Initial cost	Low	Medium	High	Very high	Low
Operating cost	Low	High	Medium	High	Low
Cost per sample	Low	Medium	Low	Medium	Low

Among these various comparisons the most important practical aspects of each method are probably detection limit followed by interferences, dynamic range and precision. As shown in Table 3 below, detection limits vary from element to element and method to method, but for the elements that are typically considered to be the most important to the herbal supplement industry (arsenic, cadmium, lead, and mercury) ICP-MS, except for cost, is the best technique and is becoming more

[36] Information in Tables 2 and 3 extrapolated from: Tyler G. ICP-MS, or ICP-AES and AAS? – a comparison. Varian Australia Pty Ltd. April 1994 (https://www.varianinc.com/media/sci/apps/icpms01.pdf accessed on December 30, 2008); and from: Anon. Guide to Inorganic Analysis. 2004. PerkinElmer, Inc. (http://las.perkinelmer.com/content/Manuals/GDE_InorganicAnalysis.pdf accessed on December 30, 2008). XRF data supplied by Dr. Peter Palmer of San Francisco State University, personal communication October 5, 2008.

commonly used for elemental analysis of dietary supplement products and ingredients. It has the best linear range for the elements of interest with few interference problems that have been further reduced with the introduction of newer generation units with dynamic reaction cells, cool plasma, and/or collision cell technologies.

Table 3. Detection Limit[37] comparisons (µg/L) or (ppb)

	FAAS	GFAAS	ICP-AES	ICP-MS	XRF
Arsenic	150	1	20	<0.05	1000
Cadmium	0.8	0.002	0.1	<0.05	50,000
Lead	15	0.5	1	<0.05	5000
Mercury	300	0.6	1	<0.05	5000

Recent California Proposition 65 settlements have prescribed ICP-MS or GFAAS for measuring lead.[38] More recently analysis was limited to ICP-MS, except "in the event that equally or more accurate testing methods are developed or identified and accepted by the scientific community as accurate."[30] If a laboratory can meet the requirements of recovery, precision, ruggedness, limit of detection, linearity, and range (as can be routinely done with ICP-MS instrumentation) it can use any technique it wishes. FDA has not specified by regulation any specific technique for heavy metal analysis for any food or dietary supplement product, though it is usual for the analytical chemists employed there to use modern technology. Consequently it may be that ICP-MS would be the technique favored by FDA for any analysis that it performs on foods or dietary supplements.

[37] For FAAS, ICP-AES, and ICP-MS the detection limit is defined on the basis of 3 standard deviations of the blank. For GFAAS sensitivity (0.0044 absorbance) is measured with 20µl of sample. XRF data supplied by Dr. Peter Palmer of San Francisco State University, personal communication October 5, 2008.

[38] Superior Court of the State of California, County of Los Angeles. *People of the State of California v. Alpro Alimento Proteinicos., S.A. de C. V. et al*. July 9, 2004.

Determining your testing needs

What metals do I need to test for?

Arsenic, cadmium, lead, and mercury are the four heavy metals most commonly tested for in dietary supplement products.

Laboratories that test for heavy metals, whether within a manufacturing facility or serving on a contractual basis, often can perform testing for other non-heavy metals including active ingredients in a product. For example, testing methods and equipment used to detect and quantify heavy metals are often also well suited for testing trace elements. Nontoxic forms of some elements such as chromium (Cr) and selenium (Se) are sometimes added as trace minerals to supplements and are thus found at relatively low levels within the raw ingredients containing them and in the final products. Additionally, macrominerals such as calcium (Ca), phosphorus (P), and magnesium (Mg) are often added to supplements and can be quantified using methods similar to those used for heavy metals, but need to be significantly diluted to fit their linear calibration/quantitation range. These minerals may often also be quantified from the same sample preparations used for heavy metals or trace minerals with the final analysis performed on a different instrument, such as ICP-MS for trace analytes and ICP-AES for elements in higher concentrations.

What detection limits do I require?

Detection limits represent the smallest amount of a substance, in this case an individual metal, which can be seen but not accurately measured by a particular method. The smallest amount of a substance that can be routinely measured is often called Limit of Quantitation (LOQ). When communicating with your in-house or contractual lab, be aware that different labs apply different meanings to the term "detection limits." Some of the most commonly used are Practical Quantitation Limit (PQL), Reporting Limit (RL) also sometimes known as Level or Limit of Detection (LOD), and Method Detection Limit (MDL).[39]

As was shown in the previous section, detection limits are very much determined by the specific analytical instrumentation used. As a general rule, the lower the detection limit the more complex the method, which in turn limits the number of laboratories offering the service. Regulatory limits are often the main reference for

[39] The MDL provides 99% confidence that the data can be differentiated from background noise. The PQL is an estimated value usually between 3 to 10 times the MDL. The RL is between these limits but always greater than or equal to the lowest calibration standard. It is equivalent to the LOQ for this discussion.

determining the detection limits required for a particular product. Regulations may be prescriptive in terms of which metals must be tested and what the allowable levels of these metals are within a material.

In any event, when consulting with an analytical lab to determine the levels of heavy metals in ingredients or products, make sure that the detection limits of the method they employ are sufficiently sensitive to measure the metals at the levels established in your specifications.

And since heavy metal limits set in product specifications may be based on daily exposure amounts, the minimum analytical detection limits required for a particular metal vary based upon the recommended serving sizes associated with individual products. Products with larger serving sizes (e.g., 3 grams vs. 250 mg) may require lower detection limits to be reached for the ingredients in those products. Make sure that the analytical lab responsible for testing your products, whether in-house or contractual, is informed of the specifications that need to be accommodated so that methods with sufficient sensitivity are employed.

What type of sample matrices will I need tested?

This is an important question because the type of material that is being tested will help dictate which testing methods and facilities are appropriate. The sample matrix will need to be communicated to the test facility prior to conducting a test for a particular heavy metal or metals because the test sample must be manipulated into a form that is suitable for the method. Different sample matrices, such as capsules, gel caps, tablets, powders, etc. may require different sample preparations to suit a particular method of analysis. For instrumental methods such as FAAS, GFAAS, ICP-AES, and ICP-MS the sample generally must be made available in liquid form. Most often this entails a type of digestion process, as discussed earlier. At a minimum the testing facility should have knowledge of your sample matrix materials and possess the equipment, reagents, methods, and procedures to properly process your sample prior to and during testing.

How quickly do I need the results?

If using an outside laboratory knowing your business model and considering how likely you are to need rush vs. standard turn around times (TATs) will aid in your selection of a testing facility. Within a quotation for services, many laboratories provide a sliding scale of TATs with associated pricing. Typically, the shorter the TAT the higher the service price will be. Some facilities may be unable to accept rush requests if their instrumentation or staffing is limited. Base pricing is often tied to a

standard TAT which varies between laboratories. Standard TATs for heavy metals testing can be as short as a few days to as long as several weeks, depending upon the testing facility. Some facilities will offer quicker TATs on a case-by-case basis depending on the sample workload at the time of the request. Premium charges are usually applied to rush services but may be worth the investment if it means quicker release of a finished product or production material. In-house testing requires appropriate allocation of people and equipment. These needs must be considered, though an in-house facility is obviously under more control than an outside source.

Once you understand your needs, you can go about selecting a testing facility or designing in-house procedures that will meet those needs. By comparing your answers from the questions above to the capabilities of a potential laboratory, you can begin the screening process, if choosing a contract laboratory, by making sure that the facility has the proper testing equipment and can provide you with results in a suitable timeframe. The next logical step in the selection process is assuring that the testing facility can consistently produce accurate results and defensible data. This may be accomplished by asking the laboratory a series of questions, either verbally or in a written form such as a "desk audit."

A desk audit is nothing more than a series of written questions related to methods, quality, certifications, etc. delivered to a testing facility. The audit document usually requires the signature of someone from the testing facility attesting to the accuracy of the information provided. This signature offers a limited sense of security in terms of minimizing liability in the event of inaccurate testing.

Choosing a laboratory to do heavy metals testing

Once a decision has been made to test finished products or raw materials for heavy metals by a contract laboratory, a more challenging aspect of the decision may come into play – which laboratory should perform the testing? Some manufacturing companies are equipped to conduct all or most of their analysis in their own laboratory facility, and many more have expressed their intention to add such facilities in the near future. But other manufacturers will instead rely on outside labs, and this section is specifically relevant to firms that expect to work with a contract analytical lab.

Most labs perform some sort of testing but not all offer heavy metals testing with the desired limits of detection and quality that your business may need. The task of finding an analytical lab can be overwhelming to those unfamiliar with the technical intricacies of trace elemental instruments, methods and associated regulations. However by asking the proper questions while knowing and conveying your needs, choosing an appropriate lab will help assure that you get usable and legally defensible data while being mindful of your quality assurance (QA) budget.

It pays to take the time to determine your needs prior to talking with an analytical laboratory, as these needs will ultimately drive your laboratory selection. AHPA previously published an article on how to choose a contract analytical laboratory. Available online[40] it is still useful though the current article is geared to heavy metal analysis in particular.

Questions to consider asking a potential testing laboratory

Is the facility accredited, certified or registered with a regulatory body?
Herbal and other dietary supplement testing does not require the use of an accredited laboratory. However, using a lab that has an external 'stamp of approval' from an outside agency may be a good indicator that the lab has the basic aspects of a quality assurance program in place. Be aware that there are no certifications specifically available for laboratories performing heavy metals testing of dietary supplements or herbal products. Laboratories can, however, be certified through other programs (such as environmental programs) which, depending upon the program, can offer some assurances as to qualifications of testing personnel, instrument calibration and maintenance procedures, facility infrastructure (hoods,

[40] http://www.ahpa.org/Portals/0/pdfs/03_0915_NPI_Contract%20Lab.pdf accessed on December 23, 2008.

clean rooms, etc.), and the ability to correctly analyze blind or unknown samples provided by the certifying agency.

The National Environmental Laboratory Accreditation Program (NELAP) uses state and federal environmental agencies, with coordination by the EPA, as accrediting authorities for laboratories. While there is no provision within the scope of accreditation that directly references dietary products, the criteria for accreditation is based primarily on two documents from the International Standards Organization (ISO), ISO/IEC Guides 25 and 58. Implementation of these standards serves to maintain a general quality system and technical requirements that are applicable to all labs regardless of the materials that they test. California Proposition 65 references, but does not mandate, laboratory accreditation through the NELAP program or California's reciprocal Environmental Lab Accreditation Program (ELAP).

Does the laboratory perform the testing in-house?
Laboratories will at times accept samples for testing that will, in-turn, be sent to another lab for the actual analysis. This is done in an effort to provide a more comprehensive list of services to their clients. While this is an accepted procedure, and not inherently wrong, it does place the control of your sample into the hands of more than one lab. When this is the case, a laboratory should always make their direct customer aware of the fact that testing will be subcontracted and provide the name of the subcontract facility. A lab should also have a written policy for selecting and evaluating potential subcontractors, and be willing to share it with their customers.

How does the laboratory assure that the methods used are suitable for the particular matrix being tested?
At a minimum, a laboratory should have a policy of performing a routine number of matrix spikes on the samples being tested. A matrix spike is accomplished by adding a known amount of the element(s) to be tested directly to the sample. The laboratory then analyzes the sample and the matrix spike independently and assesses their ability to recover the added spike from the sample. Laboratories should have written acceptance limits for the recovery and have procedures in place to handle situations where the recovery is outside these limits. If you are offering a new matrix to a laboratory for the first time, it may be beneficial to request a matrix spike be done on your specific sample. Be prepared, however, to pay an additional charge for such special requests.

Some laboratories will offer method validation services specific to unique sample matrices. Validation activities vary but generally include running replicate samples and matrix spikes through the full analytical process often at slightly varied conditions to verify method reproducibility, detection limits, ruggedness, etc. Such services come at premium pricing but need only be done once to confirm method suitability.

Does the laboratory operate under a structured quality assurance program?
A quality control program should at a minimum consist of maintenance of a quality manual that addresses critical aspects of laboratory operations. This manual usually contains information about the ownership and goals of the laboratory as well as the staff organization and responsibilities. Procedures either within the manual or supplemental to the manual should also be available for sample control and documentation, individual analytical methods, analyst training, equipment preventive maintenance, calibration, corrective actions, internal quality control activities, audits, and data assessment reduction, data validation, and data reporting. A copy of the quality manual and a list of other available procedures should be made available to potential clients at their request. All documents should be made available for review if an on-site audit is agreed upon.

Will the laboratory provide supporting information if requested?
Along with test results, the laboratory report should include at a minimum a description of the sample being tested, the dates of sample receipt and test completion, the method used for testing, and the detection limit associated with each test. While this is adequate for most testing needs there are times when additional information may be desired. For instance, information on the recovery of a matrix spike and the result of associated laboratory blanks may be useful in explaining a result which appears anomalous. Laboratories should be able to provide this information at the time of report generation or subsequently by accessing the raw testing data.

Does the facility have Out of Specification (OOS) and Non-Conforming Product (NCP) procedures in place?
OOS procedures direct the efforts of a laboratory when a sample result is outside of a range provided by the client for a particular sample or product. Many labs have a general procedure for handling OOS situations which involve client communication and repeat analyses. The OOS procedure should also address what to do if repeat analyses produce results different from the original. In some cases it may be

appropriate for the results to be averaged while other situations may call for all results to be reported individually. In some instances labs may decide to drop one, or several, of the results and report the others. As the customer, you may want to direct the laboratory's efforts with regard to these activities.

NCP procedures describe how a laboratory handles situations when a mistake is made or when work is not in conformance with lab or client specifications. Unfortunately mistakes can happen in even the most controlled situations, so it is important that clients are informed promptly when errors occur and are comfortable with the practices involved in the resolution of the problem.

Does the facility routinely measure Proficiency Testing (PT) samples?
PT samples (sometimes called "blind samples") are materials which contain target analytes (e.g., lead, cadmium, etc.) that can be purchased through commercial providers or obtained from regulatory agencies as part of their accreditation protocols. The amount of each analyte in a PT sample is known only to the provider and is not made available to the testing facility. The laboratory analyzes the samples, preferably as part of their normal routine, and reports the results to the PT provider. A report is then generated by the PT provider comparing the generated results to the target values and associated acceptance ranges. Regular participation in a PT program helps demonstrate analytical competence and shows a commitment to managing laboratory performance.

Does the facility use commercially prepared reference materials?
Standard Reference Materials (SRMs) are substances which are homogeneous and contain well established analyte amounts. These materials have often been verified by several laboratories using different analytical techniques so that they can be confidently used to calibrate instruments or assess the accuracy of an analytical method. The use of commercially prepared SRMs helps assure the accuracy of critical points in the method, such as instrument calibration. The National Institute of Standards and Technology (NIST) is a common source of SRMs of various types, many of which are more closely related to herbal products than others offered in the marketplace.

How does the laboratory assure samples are not being contaminated during processing?
Heavy metals analysis often involves the quantitation of elements in the microgram or even nanogram range within a sample. At levels this small it is quite possible for sample contamination to occur during the course of sample preparation or analysis. Contamination can occur from the environment, the reagents, the apparatus, and

even the analyst. Controls should be in place to minimize the potential contamination from all these sources and a monitoring program in place to recognize contamination if it occurs.

In the metals laboratory, contamination monitoring is accomplished most often by processing a method blank along with a set of samples. A method blank is a substance, usually deionized water that does not contain the element of interest. This material is treated like a sample in terms of processing, in that it receives the same amounts and types of reagents and is processed through the same instruments, by the same analysts, etc. as the associated samples. Any contamination which would affect the samples should be evidenced in the analysis of the method blank. Results of the method blank are not routinely reported but should be made available upon request. The detection limit for a particular element should always be above the level of that element in the method blank.

Does the laboratory have experience in the type of testing you need?
As the saying goes, "practice makes perfect!" Scientists will be quick to note that nothing is perfect, but there is certainly value in experience, especially when it involves the use of highly technical pieces of scientific equipment. Labs that have extensive experience with herbal and other dietary supplement products have the advantage of knowing the solubility of these materials, which in turn helps in the selection of digestion techniques for various metals. They may also be aware of common interferences within the matrices that can be overcome by small method modifications, such as monitoring alternative isotopes during ICP-MS testing. All of these can add up to time and cost savings for the laboratory and the client.

Will the laboratory provide the results in the desired units of measure?
The analyst producing the results may automatically know that ppm, µg/g, ng/mg, and mg/kg are all the same thing, but not all clients do! If your specifications dictate that a product contain less than 5 ppm of arsenic, ask your lab to use ppm units when reporting results. If the sample or serving size is provided to the laboratory, the lab may agree to report the results in amount per serving such as mg/tablet, µg/20 ml, etc. This is important in meeting heavy metal final product limit specifications based on the amount of heavy metals present in a serving size, not their concentration in the finished product. These small types of report customizations can save you time and may prevent accidental misinterpretation of results.

What are some other considerations when choosing an analytical lab to perform your heavy metals testing?

If time and funds permit, consider visiting the testing facility to conduct an on-site audit. Spend time talking with the analysts who perform the testing and ask to see the raw data for a material similar in nature to the one you are thinking of sending. Laboratories commonly assign unique numbers to samples which will allow you to look at testing data without compromising another client's confidentiality.

Consider evaluating and selecting a back-up laboratory. A second lab may come in handy in the event of a problem arising in the primary lab. Large projects have been known to overwhelm a facility causing turnaround times to increase and limit a lab's ability to respond to rush needs. A second facility can often help in these types of situations. Provide the laboratory with as much information as you can about your sample. Talk with them about the active ingredients (e.g., chromium polynicotinate vs. chromium chloride) and anticipated levels of known constituents. This type of information will help the lab select appropriate techniques and dilution ranges which will speed sample processing sample and get the results in your hands more quickly.

AHPA guidance on maximum quantitative limits for heavy metals in herbal supplements

Dietary supplement manufacturers determine what, if any, tests or examinations are appropriate for their products, whether to meet specifications established for these products or for other purposes.

With respect to herbal supplements, there are a variety of heavy metals for which companies may consider implementing tests or examinations, if appropriate. This guidance discusses some of the more commonly used ones. Not all of these, however, are applicable to every herbal supplement, and others not included here may be relevant for some such products.

Where manufacturers choose to establish one or heavy metal specifications for herbal supplements, AHPA provides as guidance on maximum quantitative the limits recorded in Table 4 below.[41]

In determining the specific limits identified by this guidance, AHPA compiled heavy metal limits established by various national and international organizations, presented as tables in the appendix to this document, and reviewed these in light of their scientific and regulatory origins. Consideration was also given to possible analytical challenges and to in-house industrial knowledge of heavy metal levels in raw materials and finished products.

[41] These limits may also be applicable to food products, such as tea and juice products, as well as herbal supplements.

Table 4. AHPA guidance on maximum quantitative limits for orally consumed herbal supplements

	Arsenic (inorganic)	Cadmium	Lead	Methylmercury
Limit (µg/day)	10	4.1	10	2.0

For purposes of this guidance the following definition applies:

- "Herbal supplement" *means* a dietary supplement, as described in 21 U.S.C. 321 (ff), that contains one or more herbal ingredients (i.e., an herb or other botanical, or a concentrate, extract, or combination of an herb or other botanical). An herbal supplement may or may not contain additional non-herbal dietary ingredients (e.g., vitamins, minerals, amino acids, etc.) or excipients.

In addition, for purposes of this guidance the following limitations and conditions apply:

- This guidance is not intended to suggest that manufacturers should establish specifications for any or all of the identified heavy metals in any specific herbal supplement, but is rather intended to provide guidance for limits in the event any such specifications are set. This guidance is not, in fact, applicable for some herbal supplements. In addition, it may not be relevant to test any specific herbal supplement to determine the level of any or all of the heavy metals identified in this guidance.
- The above quantitative limits are determined at the highest labeled dose of a supplement, and are applicable only to herbal supplements that are consumed in a total daily amount of 5 grams or less.
- A product in compliance with this guidance may require a warning in order to comply with California Proposition 65's listing of these chemicals.

In using this guidance, manufacturers of dietary supplements should understand that each of the quantitative limits in this guidance is intended to be used only if the manufacturer establishes a specification for the specific heavy metal to which a limit applies. This guidance does not, however, recommend that specifications be established for all four of these heavy metals for each and every dietary supplement produced. A manufacturer's responsibility is to establish specifications "on those types of contamination *that may adulterate or may lead to adulteration* of the finished batch of the dietary supplement to ensure the quality of the dietary supplement"[42] (emphasis added). A specification may therefore need to be established, for example, for inorganic arsenic in products that contain hijiki seaweed (*Hizikia fusiformis*), since that particular plant has been reported to be a possible source of high levels of inorganic arsenic.[12] But there would be no need to establish a specification for this chemical in herbs in which arsenic is not observed. In determining when to set specifications for heavy metals (as with all specifications under cGMP) manufacturers should keep in mind that FDA will conduct their inspections with the

[42] 21 CFR 111.70(b)(3).

assumption that any specification that is established is one that must be met,[43] and that the manufacturer is prepared to demonstrate that all specifications have, in fact, been met.

It should also be noted that AHPA does not intend, by this guidance, to discourage any manufacturer from setting specifications for heavy metals at lower levels if such lower levels can be met by selective use of raw materials with least feasible levels of these four heavy metals. AHPA thus supports FDA's expressed policy of "reducing lead levels in the food supply to reduce consumers' lead exposure to the lowest level that practically can be obtained."[44]

In limiting this guidance to dietary supplements consumed at daily levels below 5 grams and acknowledging that the use of some specific herbs may require higher limits, AHPA's guidance recognizes the pragmatic difficulty in setting a standard for all supplement products. These allowances envision, however, that the level of heavy metal exposure should be kept to a minimum while still allowing manufacturers to find or develop adequate sources of raw materials, and assume that exceptions are implemented only when consumer safety may be assured through short term use or other mitigating factors.

The rationale behind each of the limits recorded in Table 4 is explained below on a metal by metal basis. When relevant, some discussion is also provided on analytical processes and on one or another of the limitations identified in Table 4. Note that when references to limits set by other organizations are included in the Appendix to this document, they are not repeated in this section.

Arsenic

In its most recent evaluation of arsenic, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable weekly intake (PTWI) of 15 µg/kg body weight for inorganic arsenic. In working to develop the standard that is now identified as NSF/ANSI 173 (2008), NSF International reviewed the JECFA PTWI and chose this limit to derive a limit for arsenic in dietary supplements under NSF/ANSI 173 because "WHO had performed a comprehensive risk assessment on arsenic."[45] NSF allocated an arbitrary portion of 10 percent of total daily arsenic

[43] 21 CFR 111.73 and 111.75.

[44] 70 FR 76462.

[45] Anon. Dietary Supplement-Standard 173; Metal contaminant acceptance levels, page 6. September 3, 2003. NSF International.

intake to a dietary supplement, and, through a series of rounding calculations, arrived at a limit of 0.01 mg/day (10 µg/day) for a 60 kg person.

The Canadian Natural Health Products Directorate's (NHPD's) limit for arsenic and its salts present in a natural health product is stated as 0.14 µg/kg body weight, and was "calculated by dividing NSF limit of 0.01 mg/day by 70 kg."[46] Reversing this calculation (i.e., multiplying by 70 kg) results in a daily limit of 10 µg/day for a 70 kg adult. Note that although this limit is stated as specific to "arsenic and its salts," without differentiation as to species, the calculations for this limit were derived from limits for inorganic arsenic. AHPA therefore assumes that Canada's limit is intended to be for inorganic arsenic.

In establishing the maximum quantitative limit of 10 µg/day for inorganic arsenic incorporated in this guidance, AHPA is following the precedent of NSF/ANSI 173 and Canada's NHPD. AHPA thus also assumes a dietary supplement source contribution of 10 percent of total daily exposure to inorganic arsenic (and in fact for each of the other heavy metals discussed here), with the balance consumed in the remainder of the diet. Initial response from industry indicates that it appears generally feasible to meet this 10 µg/day recommended limit in finished herbal supplement products, although sea vegetables and certain other herbs may require higher allowances.

As noted in Table 1d, California's OEHHA has established an NSRL (no significant risk level) for arsenic as a carcinogen at 10 µg/day and, though also listed under Proposition 65 as a reproductive toxin, has not yet set an MADL (maximum allowable daily level) to address that concern. It should be noted that OEHHA's NSRL is specified for "arsenic," even though the relevant listing is for "arsenic (inorganic arsenic compounds)." It should also be noted that settlements of Proposition 65 complaints have included limits of "10.0 micrograms/day of arsenic," which must be assumed to be total arsenic. Thus, and as noted in the limitation on AHPA's limits for heavy metals delineated in Table 4, companies that sell products in California and that comply with AHPA's recommended limit for inorganic arsenic may still need to provide a clear and reasonable warning if the total arsenic in a product exceeds the level that would require such warning.

Because the determinations of inorganic arsenic from total arsenic requires additional analysis, companies may first test for total arsenic and, if warranted – i.e., if the

[46] Kyeyune V and Marles R. Organic and inorganic arsenic in Natural Health Products; Issue Analysis Summary (IAS). May 20, 2008.

amount of total arsenic in a daily serving of a supplement exceeds 10 µg – follow up with more sophisticated testing to determine the amount of inorganic arsenic.[47] The additional analytical work required to speciate these elements can involve method development for each matrix, which could represent a substantial financial investment.

Of additional interest in reviewing botanical sources of arsenic, current research indicates that while sea vegetables contain significant levels of arsenic, only hijiki has so far been shown to contain high levels of inorganic arsenic.[12, 48] Consequently, it may be reasonable for companies to establish separate specification levels for total arsenic in sea vegetable containing products. Of relevance to this is the fact that the European Pharmacopoeia 5.0 has established a total arsenic maximum content of 90 ppm for kelp.[49] Other individual herbs may also require higher allowances, which should be justified by the manufacturer.

Cadmium

AHPA's approach to setting an maximum limit for cadmium was similar to that described for inorganic arsenic, except that after reviewing other standards and noting that the actual presence of cadmium in herbs is rarely observed, a decision was made to adopt the MADL set under California's Proposition 65.

The JECFA PTWI for cadmium is 7 µg/kg body weight. NSF International noted that JECFA had "examined data on the dietary intake of cadmium in a wide variety of countries" and investigated "the chemical identity and bioavailability of cadmium in foods."[50] NSF/ANSI 173 therefore set a limit of 6 µg for finished supplement products, derived by calculating the daily level of the JECFA PTWI for a 60 kg adult and assigning a 10 percent source contribution. Canada's NHPD's limit for cadmium in finished natural health products is also 6 µg. California's MADL for cadmium is 4.1 µg/day, and the NSRL for this chemical is only relevant to inhaled cadmium.

In establishing the limit of 4.1 µg/day for cadmium incorporated in this guidance, AHPA has chosen to adopt the lower limit set by OEHHA in California. Consultation

[47] Ion Chromatography combined with ICP-MS allows the separation of the common forms of arsenic prior to quantitation by ICP-MS.

[48] Nakamura Y, Narukawa T, and Yoshinaga J. Cancer risk to Japanese population from the consumption of inorganic arsenic in cooked hijiki. *J Agric Food Chem* 2008; 56(7):2536-40.

[49] Fragmented dried thallas of *Fucus vesiculosus*, *F. serratus*, or *Ascophyllum nodosum*.

[50] Footnote 45, page 9.

with dietary supplement manufacturers indicates that this level appears to be generally feasible for finished products.

Some herbs are known bioaccumulators of cadmium and may require higher allowances, which should be justified by the manufacturer.

Lead

Following the approach described above for arsenic and cadmium, the JECFA PTWI of 25 µg/kg body weight serves as the starting point for evaluating an acceptable limit for dietary supplement finished products. Citing NSF International again, "the JECFA number was selected for the acceptable limit derivation [for NSF/ANSI 173] because human exposures from around the world were taken into account and a Monte Carlo Analysis was performed that more accurately defines the extent of harm in an exposed population."[51]

Converting the PTWI to a daily limit for a 60 kg adult NSF/ANSI 173 and subsequently Canada's NHPD have adopted limits of 20 µg/day from any individual finished product. In consultation with member companies, AHPA found that a limit of 10 µg/day is generally feasible for supplement products, and so has adopted that lower maximum level.

In establishing this maximum limit, AHPA recognizes that it may not be appropriate for products intended for ingestion by children and pregnant women.

As noted in Table 1d, while California's OEHHA has established an NSRL (no significant risk level) for lead at 15 µg/day, the MADL for lead is just 0.5 µg/day. Thus, and as noted in the limitation on AHPA's quantitative limits for heavy metals delineated in Table 4, companies that sell products in California and that comply with the maximum limit given here for lead may still need to provide a clear and reasonable warning if the lead present in a product exceeds the level that would require such warning.

Mercury

Both JECFA and the Agency for Toxic Substances and Disease Registry (ATSDR) within the U.S. Department of Health and Human Services address mercury specific to its more toxic organic form, methylmercury. The JECFA PTWI of 1.6 µg/kg body weight calculates to 16 µg/day in a 70 kg adult, while ATSDR's minimal risk level

[51] Footnote 45, page 16.

(MRL) for chronic oral consumption of 0.3 µg/kg body/day equates to 21 µg/day for the same adult. AHPA has adopted an maximum limit of 2.0 µg for dietary supplements, representing approximately 10 percent of these daily limits for all sources, and AHPA believes, based on input from member companies, that this limit is generally feasible for supplement products.

In establishing this limit, AHPA recognizes that lower levels may be appropriate for products intended for ingestion by particularly sensitive populations, including children and women who are pregnant or may become pregnant.

Neither an MADL nor an NSRL has been established for methylmercury in relation to its listing under California's Proposition 65. Of interest to marketers in that state, however, is the fact that settlements of Proposition 65 complaints have included limits of 3.0 µg/day of inorganic mercury, and a lower limit of 0.3 µg/day of "mercury and mercury compounds, except inorganic mercury." To repeat once again, and as noted in the limitation on AHPA's maximum quantitative limits for heavy metals delineated in Table 4, companies that sell products in California and that comply with AHPA's recommended limit for methylmercury may still need to provide a clear and reasonable warning if the amount in a product exceeds the level that would require such warning.

Thus, and as noted in the limitation on AHPA's guidance on heavy metals limits delineated in Table 4, companies that sell products in California and that comply with AHPA's recommended limit for lead may still need to provide a clear and reasonable warning if the lead present in a product exceeds the level that would require such warning.

As discussed in the above section on arsenic, and because AHPA's mercury-related maximum limit is specific to a form of mercury rather than to total mercury, companies may first test for total mercury and only conduct secondary analysis for methylmercury if the amount of total mercury in a daily serving of a supplement exceeds 2 µg.[52] As with any more sophisticated testing, companies must evaluate the additional financial cost of speciated analysis.

[52] Liquid Chromatography combined with ICP-MS can provide methylmercury and inorganic mercury results within a single analysis.

Note on relation between concentration and consumption levels

A coordinated effort between ingredient suppliers and dietary supplement manufacturers is essential to meet finished product specifications, since heavy metal limits for raw material need to take into account the serving size as stated on a finished product label. Ingredient suppliers may not have this information, so any heavy metal limit specifications for the final product need to be communicated from manufacturers to their suppliers so that ingredient specifications can be set appropriately.

AHPA previously provided guidance to members regarding California Proposition 65 with respect to heavy metals.[53] This document included a section for calculating the delivered dose of heavy metals in a supplement serving size based on the concentration of heavy metals present. Table 5 below borrows from that document. Maximum concentration in parts per million are given over a range of daily serving sizes for each of the heavy metals addressed in Table 4.

[53] Footnote 9.

Table 5. Serving size in relation to presence of heavy metals

	Limit (µg)	Maximum concentration (ppm) at highest labeled daily consumption rate										
		.25g	.5g	1g	2g	2.5g	3g	4g	5g	6g	8g	10g
Arsenic (inorganic)	**10**	<40	<20	<10	<5.0	<4.0	<3.0	<2.5	<2.0	<1.7	<1.2	<1.0
Cadmium	**4.1**	<16	<8.2	<4.1	<2.0	<1.6	<1.3	<1.0	<0.82	<0.68	<0.51	<0.41
Lead	**10**	<40	<20	<10	<5.0	<4.0	<3.0	<2.5	<2.0	<1.7	<1.2	<1.0
Methylmercury	**2.0**	<8.0	<4.0	<2.0	<1.0	<0.80	<0.67	<0.50	<0.40	<0.33	<0.25	<0.20

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Appendix

In preparing this document and in working through the process needed to establish the quantitative limits contained herein, AHPA staff and participating members reviewed various sources of heavy metal limits established by national and international organizations. These are presented in tables in the appendix that follows, organized into one table each of arsenic, cadmium, lead, and mercury. Most of the limits identified here have been established in µg per kg of body weight over a specific time (either a day or a week), others are set in µg per a defined unit of consumption, while only two of the cited entities state limits in µg per day references. In order to standardize the tables to a common factor of µg per day, arithmetic calculations were made to arrive at the daily exposure represented for each heavy metal under consideration, either by multiplying by 70 kg to convert from those limits expressed in terms of body weight, or by standard consumption quantities when limits were set on concentration in a unit of measure.

Established oral limits for ARSENIC (µg/day)

		µg/day	Notes	Reference
Limit for finished product: daily dose	**AHPA**	10	Maximum quantitative limit for "inorganic arsenic" in a dietary supplement.	AHPA Executive Committee action, November 16, 2009.
	NSF/ANSI 173	10	Maximum level of undeclared "arsenic."	NSF International Standard/American National Standard for Dietary Supplements; Approved by the American National Standard Institute and designated as an ANSI Standard on April 14, 2008.
	Canada Natural Health Products Directorate	10	Established tolerance of <0.14 µg/kg bw for "arsenic and its salts and derivatives" multiplied by 70 kg for an adult to reflect adoption from NSF/ANSI 173.	Natural Health Products Compliance Guide, Version 2.1, January 2007.
	California Prop 65 Reproductive Toxin	None set	No Maximum Allowable Dose Level (MADL) is currently stated; a draft MADL of 0.1 µg/day for "inorganic oxides of arsenic" was listed in earlier versions of the cited reference.	Proposition 65 Safe Harbor Levels, March 2008. Note that the listed reproductive (developmental) toxin is "Arsenic (inorganic oxides)."
	California Prop 65 Carcinogen	10	No Significant Risk Level (NSRL) for "arsenic" above which warning is required.	Proposition 65 Safe Harbor Levels, March 2008. Note that the listed carcinogen is "Arsenic (inorganic arsenic compounds)," but the NSRL is for "arsenic." There is a separate NSRL of 0.06 µg/day by inhalation.
Limit for total daily consumption	**US Agency for Toxic Substances and Disease Registry (ATSDR)**	20	Minimal Risk Level (MRL) of 0.3 µg/kg bw for chronic oral consumption of "arsenic" multiplied by 70 kg for an adult.	ATSDR Minimal Risk Levels, November 2007; http://www.atsdr.cdc.gov/mrls/pdfs/mrllist_11_07.pdf.
	US Environmental Protection Agency (EPA)	20	Reference Dose (RfD) of 0.3 µg/kg bw for "inorganic arsenic multiplied by 70 kg for an adult re: chronic effects (noncancer).	EPA's Integrated Risk Information System: Arsenic, inorganic, February 1993 (last revised); http://www.epa.gov/iris/subst/0278.htm; also see: http://www.epa.gov/ttnatw01/hlthef/arsenic.html.
	US FDA Tolerable Daily Intake	130	This limit is for "inorganic arsenic," and appears to be the limit for adults (~60 k).	Guidance Document for Arsenic in Shellfish, 1993; http://www.cfsan.fda.gov/~frf/guid-as.html. Note that this document "no longer represents the current state of science and is presented here for the historical record only."
	Joint FAO/WHO Expert Committee on Food Additives (JECFA)	150	Provisional Tolerable Weekly Intake (PTWI) of 15 µg/kg bw for "inorganic arsenic" multiplied by 70 kg for an adult; divided by 7 to obtain daily limit. The cited reference discusses higher consumption of the organic form in some populations.	WHO Food Additives Series: 24; Toxicological evaluation of certain food additives and contaminants, 1989;http://www.inchem.org/documents/jecfa/jecmono/v024je08.htm.
Water	**US FDA: Bottled Drinking Water**	20	Calculated from the allowable level of 10 µg/l of "arsenic" if drinking 2 liters/day.	21 CFR 165.110
	US EPA: Drinking Water Standard	20	Calculated from the Maximum Contaminant Level (MCL) of 10 µg/l of "arsenic" if drinking 2 liters/day.	40 CFR 141.23

Established oral limits for CADMIUM (µg/day)

		µg/day	Notes	Reference
Limit for finished product: daily dose	**AHPA**	4.1	Maximum quantitative limit for cadmium in a dietary supplement.	AHPA Executive Committee action, November 16, 2009.
	NSF/ANSI 173	6	Maximum level of undeclared cadmium.	NSF International Standard/American National Standard for Dietary Supplements; Approved by ANSI and designated as an ANSI Standard on April 14, 2008.
	Canada Natural Health Products Directorate	6	Established tolerance of <0.09 µg/kg bw for cadmium multiplied by 70 kg for an adult to reflect adoption from NSF/ANSI 173.	Natural Health Products Compliance Guide, Version 2.1, January 2007.
	California Prop 65 Reproductive Toxin	4.1	Maximum Allowable Dose Level (MADL) of cadmium above which warning is required.	Proposition 65 Safe Harbor Levels, March 2008. Listing is for "cadmium" and specifies "developmental, male."
	California Prop 65 Carcinogen	-	No Significant Risk Level (NSRL) for cadmium exists only for inhalation (0.05 µg/day); no level is given for oral consumption.	Proposition 65 Safe Harbor Levels, March 2008. Note that though cadmium is listed for cancer, this chemical is not generally considered carcinogenic by the oral route.; the listing of cadmium in the Proposition 65 list does not, however, state this clearly.
Limit for total daily consumption	**US Agency for Toxic Substances and Disease Registry (ATSDR)**	14	Minimal Risk Level (MRL) of 0.2 µg/kg bw for chronic cadmium oral consumption multiplied by 70 kg for an adult.	ATSDR Minimal Risk Levels, November 2007; http://www.atsdr.cdc.gov/mrls/pdfs/mrllist_11_07.pdf.
	US Environmental Protection Agency (EPA)	70	Reference Dose (RfD) of 1.0 µg/kg bw for dietary exposure to cadmium multiplied by 70 kg for an adult re: chronic effects (noncancer).	EPA's Integrated Risk Information System: Cadmium, February 1994; http://www.epa.gov/iris/subst/0141.htm; also see: http://www.epa.gov/ttn/atw/hlthef/cadmium.html).
	US FDA Tolerable Daily Intake	55	The cited reference gives this level for cadmium, and states, "Since cadmium toxicity is expressed only after chronic exposure, separate figures for the age category 2-5 years are not warranted."	Guidance Document for Cadmium in Shellfish, 1993; http://www.cfsan.fda.gov/~frf/guid-cd.html. Note that this document "no longer represents the current state of science and is presented here for the historical record only."
	Joint FAO/WHO Expert Committee on Food Additives (JECFA)	70	Provisional Tolerable Weekly Intake (PTWI) of 7 µg/kg bw for cadmium multiplied by 70 kg for an adult and divided by 7 to obtain daily limit.	WHO Food Additives Series 52; Safety evaluation of certain food additives and contaminants; 2004; http://whqlibdoc.who.int/publications/2004/924166052X.pdf page 556.
	European Union	70	The European Commission endorsed JECFA's PTWI of 7 mcg/kg bw for cadmium on June 2, 1995; multiplied by 70 kg for an adult and divided by 7 to obtain daily limit.	2006: Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs; in the Official Journal of the European Union, 20.12.2006 (EN), L 364/5.
Water	**US FDA: Bottled Drinking Water**	10	Calculated from the allowable level of 5 µg/l of cadmium if drinking 2 liters/day.	21 CFR 165.110
	US EPA: Drinking Water Standard	10	Calculated from the Maximum Contaminant Level (MCL) of 5 µg/l of cadmium if drinking 2 liters/day.	40 CFR 141.23

Established oral limits for LEAD (µg/day)

		µg/day	Notes	Reference
Limit for finished product: daily dose	**AHPA**	10	Maximum quantitative limit for lead in a dietary supplement.	AHPA Executive Committee action, November 16, 2009.
	NSF/ANSI 173	20	Maximum level of undeclared lead.	NSF International Standard/American National Standard for Dietary Supplements; Approved by ANSI and designated as an ANSI Standard on April 14, 2008.
	Canada Natural Health Products Directorate	20	Established tolerance of <0.29 µg/kg bw for lead multiplied by 70 kg for an adult to reflect adoption from NSF/ANSI 173.	Natural Health Products Compliance Guide, Version 2.1, January 2007.
	California Prop 65 Reproductive Toxin	0.5	Maximum Allowable Dose Level (MADL) of lead above which warning is required.	Proposition 65 Safe Harbor Levels, March 2008. Listing is for "lead" and specifies "developmental, female, male."
	California Prop 65 Carcinogen	15	No Significant Risk Level (NSRL) of lead above which warning is required.	Proposition 65 Safe Harbor Levels, March 2008. Note that each of the following is listed as a carcinogen: "lead and lead compounds," "lead acetate," "lead phosphate," and "lead subacetate."
Limit for total daily consumption	**US Agency for Toxic Substances and Disease Registry (ATSDR)**	-	No Minimal Risk Level (MRL) established for lead "because a clear threshold for some of the more sensitive effects in humans has not been identified."	August 2007: ATSDR's Toxicological Profile for Lead, Draft from Public Comment; Section 2: Relevance to Public Health; page 31.
	US Environmental Protection Agency (EPA)	-	EPA has not established a Reference Dose (RfD) for lead; RfD Work Group (1985) stated "inappropriate to develop an RfD for inorganic lead." Cited reference notes it appears that some of lead's adverse effects "may occur at blood lead levels so low as to be essentially without a threshold."	EPA's Integrated Risk Information System: Lead and compounds (inorganic); July 2004 (last revised); http://www.epa.gov/iris/subst/0277.htm; also see: http://www.epa.gov/ttn/atw/hlthef/lead.html).
	US FDA Tolerable Daily Intake	75	Level here is for adults. Level is 25 µg/day of lead for pregnant women, 15 µg/day for children 7 and older, and 6 µg/day for children under 6.	1993: Guidance Document for Lead in Shellfish; http://www.cfsan.fda.gov/~frf/guid-pb.html. Note that this document "no longer represents the current state of science and is presented here for the historical record only."
	Joint FAO/WHO Expert Committee on Food Additives (JECFA)	250	Provisional Tolerable Weekly Intake (PTWI) of 25 µg/kg bw for lead multiplied by 70 kg for an adult and divided by 7 to obtain daily limit.	Safety Evaluation of Certain Food Additives and Contaminants, WHO Food Additives Series: 44; 2000; http://www.inchem.org/documents/jecfa/jecmono/v44jec12.htm
	European Union	250	The European Commission endorsed JECFA's PTWI of 25 mcg/kg bw of lead on June 19, 1992; multiplied by 70 kg for an adult and divided by 7 to obtain daily limit.	Commission Regulation (EC) No 1881/2006 of 19 December 2006; maximum levels for certain contaminants in foodstuffs; Official Journal of the EU, 20.12.2006 (EN), L 364/5.
Water	**US FDA: Bottled Drinking Water**	10	Calculated from the allowable level of 5 µg/l of lead if drinking 2 liters/day.	21 CFR 165.110
	US EPA: Drinking Water Standard	30	Calculated from the Maximum Contaminant Level (MCL) of 15 µg/l of lead if drinking 2 liters/day.	40 CFR 141.80

Established oral limits for MERCURY (µg/day)				
		µg/day	Notes	Reference
Limit for finished product: daily dose	**AHPA**	2.0	Maximum quantitative limit for ""methylmercury" in a dietary supplement.	AHPA Executive Committee action, November 16, 2009.
	NSF/ANSI 173	20	Maximum level of undeclared "mercury."	NSF International Standard/American National Standard for Dietary Supplements; Approved by ANSI and designated as an ANSI Standard on April 14, 2008.
	Canada Natural Health Products Directorate	20	Established tolerance of <0.29 µg/kg bw for "mercury and its salts and derivatives" multiplied by 70 kg for an adult to reflect adoption from NSF/ANSI 173.	Natural Health Products Compliance Guide, Version 2.1, January 2007.
	California Prop 65 Reproductive Toxin	-	A draft Maximum Allowable Dose Level (MADL) of 0.3 µg/day of "methylmercury" was listed in earlier versions of the cited reference but is not included in the current document.	Proposition 65 Safe Harbor Levels, March 2008. The listed chemicals are "mercury and mercury compounds" and "methylmercury."
	California Prop 65 Carcinogen	-	A No Significant Risk Level above which warning is required has not yet been set.	Proposition 65 Safe Harbor Levels, March 2008. The relevant listed chemical is "methylmercury compounds."
Limit for total daily consumption	**US Agency for Toxic Substances and Disease Registry (ATSDR)**	20	Minimal Risk Level (MRL) of 0.3 µg/kg bw/day for chronic oral consumption of "methyl-mercury" multiplied by 70 kg for an adult.	November 2007: ATSDR Minimal Risk Levels; http://www.atsdr.cdc.gov/mrls/pdfs/mrllist_11_07.pdf)
	US Environmental Protection Agency (EPA)	7	Reference Dose (RfD) for dietary exposure of 0.1 µg/kg bw for "methylmercury" multiplied by 70 kg for an adult re: chronic effects (noncancer); note that an RfD of 0.3 µg/kg/day is set for "inorganic mercury."	EPA's Integrated Risk Information System: Methylmercury; July 2001 (last revised); http://www.epa.gov/iris/subst/0073.htm; also see: http://www.epa.gov/ttn/atw/hlthef/mercury.html).
	Joint FAO/WHO Expert Committee on Food Additives (JECFA)	16	Provisional Tolerable Weekly Intake (PTWI) of 1.6 µg/kg bw for "methylmercury" multiplied by 70 kg for an adult and divided by 7 to obtain daily limit.	WHO Food Additives Series: 52; Safety evaluation of certain food additives and contaminants; 2004; http://whqlibdoc.who.int/publications/2004/924166052X.pdf page 615.
	European Union	16	The European Food Safety Authority adopted WHO's PTWI of 1.6 µg/kg bw of "methylmercury" on February 4, 2004; multiplied by 70 kg for an adult and divided by 7 to obtain daily limit.	Commission Regulation (EC) No 1881/2006 of 19 December 2006; maximum levels for certain contaminants in foodstuffs; Official Journal of the EU, 20.12.2006 (EN), L 364/5.
Water	**US FDA: Bottled Drinking Water**	4	Calculated from the allowable level of 2 µg/l of "mercury" if drinking 2 liters/day.	21 CFR 165.110
	US EPA: Drinking Water Standard	4	Calculated from the Maximum Contaminant Level (MCL) of 2 µg/l of "mercury" if drinking 2 liters/day.	40 CFR 141.23