Tab 4

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Item No. DS-2008-1
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Joint Committee Issue Document

NOTE: An issue document may be submitted at any time – it comprises two parts: the cover sheet (this page) and a description of the issue to be submitted to the Joint Committee (following page). A separate issue form is required for each issue submitted. Issue papers include proposals for modification of a standard, information reports (of current research, etc.) and reports of Task Forces. An issue paper shall be categorized as being for ACTION or for INFORMATION. Submitters should limit the Issue Paper to 1 or 2 pages – attachments detailing full recommendations or background information may be attached with supplementary information. The Chairperson of the appropriate Joint Committee will respond within 30 days of receipt of the issue document advising what steps will be taken. Any issue document intended for discussion at a Joint Committee meeting must be received at least 21 days prior to the meeting to ensure inclusion in the agenda.

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Please insert a check in the appropriate place to indicate if you wish the item to be considered as an action item or as an information item.

Action _____ Information ____X_____

NSF Standard(s) Impacted**: 173**

Issue Statement:

Provide a concise statement of the issue, which reference as appropriate any specific section(s) of the standard(s) that are related to the issue.

To discuss qualitative testing for Chondroitin Sulfate.

Background:

Provide a brief background statement indicating the cause and nature of concern, the impacts identified relevant to public health, public understanding, etc, and any other reason why the issue should be considered by the Committee.

In the winter of 2008, the FDA responded to adverse incident reports related to contaminated heparin (allergic reactions and several deaths). The contaminant was found to be related to or similar to chondroitin sulfate (an "over-sulfated form"). This appears to be a case of economic adulteration of a drug that was imported into the US and other countries from China. The incident brings into focus the needs of having a selective method for the determination of compounds of interest. In the dietary supplement industry, chondroitin sulfate (CS) is commonly measured using a CPC Titration method, which can easily be affected by positive interferences. Work has been done through AOAC to validate and collaboratively study an enzymatic HPLC method that is more selective than many methods, which have been employed for CS. Nonetheless, the specification/label claims of many products have been developed based on the CPC titration. Switching to the enzymatic HPLC method will lead to different (lower) numeric results based on NSF's experience with the method.

Recommendation:

If action by the Joint Committee is being requested, clearly state what action is needed: e.g., recommended changes to the standard(s) including the current text of the relevant section(s) indicating deletions by use of ~~strike-out~~ and additions by highlighting or underlining; e.g., reference of the issue to a Task Force for detailed consideration; etc. If recommended text changes are more than a half page, please attach a separate document.

No impact is expected on Standard 173 since identity testing and assay testing is already required.

Suggested action by NSF in application of Standard 173 would be to continue to employ the CPC Titration for specification/label claim determinations. However, include the use of enzymatic HPLC in a qualitative way to evaluate the sample for compounds that have similar behavior to CS in the titration. For example, ensure that dermatan sulfate is not present, etc.

Supplementary Materials (photographs, diagrams, reports, etc.):

If not provided electronically, the submitter will be responsible to have sufficient copies to distribute to committee members.
NA

Submitter _Kerri L. Levanseler Date __05-01-08

Organic and Inorganic Arsenic in Natural Health Products: Issue Analysis Summary

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2008-04-19

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1. ISSUE

Arsenic is present in the environment in both organic and inorganic forms. While organic arsenicals are generally considered to have very low toxicity, the inorganic species is widely recognized as a carcinogen in addition to causing numerous other adverse health effects following acute or chronic exposure (Environment Canada 1993; ATSDR 2007). The tolerance limit for arsenic as a contaminant in natural health products currently recommended by Health Canada's Natural Health Products Directorate (NHPD) is 0.14 µg/kg body weight/day (Health Canada 2007a). However, this limit represents total arsenic and does not distinguish between organic and inorganic arsenical compounds. This has implications for the natural health products industry as certain products may contain high levels of one or more of the relatively non-toxic organic forms of arsenic. Consequently, there are also implications for Health Canada's enforcement and compliance activities under the authority of the *Food and Drugs Act* (Justice Canada 2008a) and the *Natural Health Products Regulations* (Justice Canada 2008b) related to the detection of arsenic in natural health products at levels exceeding the tolerance limit.

2. PURPOSE/OBJECTIVE

The purpose of this document is to determine whether there is substantial scientific evidence to support separate acceptable limits for inorganic and organic derivatives of arsenic, and whether suitable analytical methodology exists to distinguish between these forms in finished natural health products.

3. BACKGROUND

3.1. Arsenic and its Derivatives

Arsenic is a naturally occurring metallic element found in the earth's crust and is therefore ubiquitous in the environment. Although arsenic is commonly expressed in terms of elemental arsenic (As), this does not fully represent the pharmacokinetic and toxicological differences of the range of arsenic compounds existing in the environment. Arsenic is rarely found in its free state (A^0) in the environment; it is widely distributed as both inorganic (-3, +3, and +5 oxidation states) and organic compounds. The inorganic species arsenite (As^{3+}) is found most commonly as arsenic trioxide, sodium arsenite, and arsenic trichloride; arsenate (As^{5+}) is found as arsenic pentoxide, arsenic acid, and lead and calcium arsenates. Common organic arsenic compounds include arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid), arsenobetaine (the most predominant organoarsenical in marine animals), arsenocholine, dimethyloxyarsylethanol, trimethylarsonium lactate, arsenosugars and arsenophospholipids (JECFA 1989). Arsenic in the environment may also result from use in pesticides (mainly methyl and phenyl derivatives of arsenic acid), mining and metal manufacturing activities (ATSDR 2006, 2007).

In soils, arsenic is present as arsenite, arsenate, and in organic forms. Therefore, these compounds may be available for plant uptake and entry into the food chain. Arsenic uptake by plants is dependent on the plant type, soil chemical composition, and concentration of soluble arsenic in the soil. In water, arsenic generally occurs in the inorganic form while seafoods generally contain organic forms. Arsenic is ubiquitous in open ocean seawater, particularly in deep waters where it is present mainly in inorganic forms which are taken up by phytoplankton, rapidly detoxified to arsenosugars and minor amounts of methylated arsenical compounds. It is likely that the arsenosugars, released by the death and decay of algae, are transformed by microbial species to yield arsenobetaine which is then ingested by marine animals (Borak and Hosgood 2007). While concentrations of arsenic in marine organisms and seaweed (kelp) are generally higher than levels in other foods, marine organisms generally contain more of the less-toxic organic forms. Methylation of inorganic arsenic occurs in a variety of organisms (Shils et al. 1999).

3.2. Analytical Methodology

Atomic Absorption Spectrophotometry (AAS) is the most common analytical procedure for measuring total arsenic in biological materials (ATSDR 2007; Almela et al. 2002). Samples may be prepared for AAS using a gaseous hydride procedure (the most common method but it does

not detect all organic forms e.g. arsenobetaine); Neutron Activation Analysis (NAA) which has the advantage that no sample digestion or separation steps are required; and hydride generation combined with Atomic Fluorescence Spectroscopy which has improved sensitivity (better than 20 parts per trillion) (ATSDR 2007).

Analysis of speciation of arsenic to quantify the different organic or inorganic species generally involves three steps: extraction, derivatization and/or separation, and detection. Due to the different chemical properties of arsenic compounds, a combination of separation procedures must be used.

The most pertinent chemical property that allows the separation of the two species has to do with the nature of the bond between the arsenic and the inorganic moieties in inorganic arsenic species and the arsenic–carbon bond in organoarsenic species. The arsenic-carbon bond is a very stable and strong bond, and this remarkable chemical stability of organoarsenic species plays an important role in the separation process of these two kinds of arsenic (Ringmann et al. 2002). In general, for the digestion of organic arsenic species (that is to break the arsenic-carbon bond in organic species and convert them into inorganic species), harsh conditions are required. For example, for the total decomposition of common organic arsenic species such as methylarsenic acid, dimethylarsenic acid, trimethylarsine oxide, tetramethylarsonium iodide, arsenocholine bromide and arsenobeatine, temperatures of 200-320^{o}C have to be used, as well as strong acid mixtures such as nitric, sulphuric, hydrofluoric and perchloric acids, with microwave irradiation and pressure (Narukawa et al. 2004). The use of acid digestion together with high temperatures and sometimes microwave irradiation under pressure enables the release of arsenic from both inorganic and organic species. This is why, in order to determine only inorganic arsenic, reagents and conditions used are kept mild so that only the inorganic species undergo a few reactions to form the analyte (arsine) whereas the organic arsenic species remain unchanged in the medium.

Examples of known separation techniques include complexation with chloride and bromide ions to precipitate the corresponding trihalide followed by its distillation, and coprecipitation with iron(III) hydroxide, cerium, zirconium hydroxides, thioanilide and nipyrolidinethiocarbamade (Sounderajan et al. 2007). The method used in The Food Chemicals Codex (IOM 2003) for the determination of inorganic arsenic (for example, in kelp), involves the reaction of the sample with ferrous chloride in acidic medium to precipitate arsenic (III) chloride, after reduction of arsenic (V) to arsenic (III), which is then distilled off at approximately 110^{o}C (note that arsenic (III) chloride has a boiling point of 130^{o}C). Reduction by zinc of the arsenic chloride followed by reaction with silver diethyldithiocarbamate produces arsine which is then assayed using colorimetry. Instead of colorimetry, stripping voltammetry has also been used following the same sample preparation methodology described above, with a significant difference being that arsenic(III) chloride is used as the analyte (i.e., there is no generation of arsine) (Zakharova et al. 2004). The method employed in the "WHO Guidelines for Assessing Quality of Herbal Medicines with Reference to Contaminants and Residues" (WHO 2007) on the other hand does not discriminate between the two kinds of arsenic species. It is based on a sample preparation which involves heating the sample in ethanol with magnesium hexahydrate, followed by ignition of the resulting dry residue to incinerate (twice if required). After this decomposition the sample is analysed in the same way as described above (colorimetric).

Extraction methodologies for arsenic species from algae using various proportions of methanol/water mixtures has been studied by van Elteren et al. (2007), who concluded that a range of solvent ratios rather than a single ratio was best due to differences in polarity of the various arsenic derivatives present. Chelation-extraction or derivatization followed by extraction techniques may also be used.

Extraction is then followed by chromatographic separation, most commonly by High Pressure Liquid Chromatography (HPLC), although there are also gas chromatographic (GC), and capillary electrophoretic (CE) methods (Akter et al. 2005; ATSDR 2007).

For detection, inductively coupled plasma-mass spectrometry (ICP-MS) or inductively coupled plasma-atomic emission spectrophotometry (ICP-AES). HPLC-ICP MS and LC-electrospray MS methods have been used to elucidate arsenic biotransformation in the brown macroalga, *Fucus serratus* (Geiszinger et al. 2001). Major arsenic species monitored in this study were arsenate, arsenite, methylarsonate, dimethylarsinate, and four arsenosugars found naturally in *Fucus*. ICP-MS has been used in several recent studies to determine residues of inorganic (e.g. arsenite, arsenate) and organic (e.g. arsenobetaine) arsenic compounds in various biological materials (Jorhem et al. 2007; Mandal et al. 2004; Shibata 1992; Smith et al. 2007; Wang et al. 2007). HPLC-ICP-AES has also been applied to analysis of inorganic and organic arsenic compounds in natural samples (Shibata 1992). A summary of the various techniques is provided in ATSDR (2007).

3.3. Physiological Role of Arsenic

The biological role and essentiality of arsenic in humans has not been clearly defined due to lack of human data. The following criteria must be met before a substance can be considered essential as a nutrient in a particular animal species: (1) it is present in all organisms for which it is essential, and (2) reducing exposure below a certain limit leads to a consistent and reproducible reduction in physiologically important functions (NRC 1999). Essentiality of arsenic to normal physiology has been documented in various animals (i.e., rats, hamsters, miniature pigs, goats and chicks). At doses of 350 - 4,500 ng/g in the diet, arsenic seems to stimulate growth in these animals (Uthus 1992, NRC 1999). Studies on arsenic-deprived rats suggest that arsenic has physiological importance in various biochemical processes, particularly methionine metabolism (Uthus 1992 and 2003). Arsenic may also play a role in gene expression (IOM 2006).

Since the physiological role of arsenic in humans is not known well enough, neither an estimated average requirement, recommended dietary allowance, nor adequate intake could be established. Clarification is needed on the essentiality of arsenic for optimal health in order to establish safe and adequate intake levels (Shils et al. 1999; NRC 1999; IOM 2001; IOM 2006), although an estimated safe and adequate daily intake for arsenic of 12-40 µg/day based on animal and human studies has been proposed (Uthus 1994 in California Environmental Protection Agency 1996).

3.4. Metabolism of Arsenic

The complete metabolic detoxification pathway for inorganic arsenic in mammals has not yet been elucidated. However, arsenic biotransformation in vivo is found to occur in many species

by two main types of reactions: (1) reduction of pentavalent to trivalent arsenic, and (2) oxidative methylation reactions in which trivalent forms of arsenic are sequentially methylated. Methylation occurs by transfer of methyl groups from S-adenosylmethionine. Absorbed inorganic arsenate (As5+) is reduced to arsenite (As3+), which is transferred to the liver where it is methylated to less reactive organic metabolites such as monomethylarsonous acid (MMA) and dimethylarsinate (DMA). MMA and DMA are rapidly excreted in urine (Vahter 1994; JECFA 1983; Shils et al. 1999; WHO 2001). As a result, inorganic arsenic and its methylated metabolites have a relatively low rate of bioaccumulation. However, more research is required to determine the extent of inorganic arsenic bioaccumulation in humans, in part through improved biomarkers of exposure (Hughes 2006, Abernathy et al. 1999).

There is no data on tissue distribution of arsenic in humans following ingestion of the organic arsenic derivatives present in fish and seafood (ATSDR 2007). There are no reports of toxicity in humans from consumption of organic arsenic in seafood. Limited data are available for rats indicating that weanling rats fed 3 mg/kg bw/day arsenic in fish for 42 days did not develop treatment-related toxic effects (Siewicki 1981; JECFA 1989 and 1983).

It is generally accepted that the arsenic-carbon bond is quite strong and most mammalian species do not have the capacity to break this bond; thus, inorganic arsenic is not formed during the metabolism of organic arsenicals. In most species, including humans, ingested (or exogenous) MMA(V) and DMA(V) undergo limited metabolism, do not readily enter the cell, and are primarily excreted unchanged in the urine (ATSDR 2007).

Arsenosugar is a term used for carbohydrate compounds containing arsenic. Arsenosugar metabolism results in at least 12 metabolites being excreted in the urine, including DMA as the major metabolite (67%), thio-dimethylarsenoacetate (19%), thio-dimethylarsenoethanol (10%), oxo-dimethylarsenoethanol (4%) oxo-dimethylarsenoacetate (2%), trimethylarsine oxide (0.5%), thio-arsenosugar, other trace metabolites and unmetabolized arsenosugar (Ma and Le 1998; Francesconi et al. 2002; Raml et al. 2005). As stated previously, neither MMA nor DMA are demethylated to yield inorganic arsenic in humans (ATSDR 2007).

Ingestion of arsenic-containing lipids from cod liver resulted in metabolism in humans primarily to DMA with lesser amounts of oxo-dimethylarsenopropanoic acid, thio-dimethylarsenopropanoic acid, oxo-dimethylarsenobutanoic acid, and thio-dimethylarsenobutanoic acid. Unchanged arsenobetaine accounted for up to half of the remaining urinary arsenic (Schmeisser et al. 2006).

3.5. Toxicology

Arsenic and its inorganic compounds have been documented to be carcinogenic in humans and are therefore considered to be “toxic” as defined in section 11 of the Canadian Environmental Protection Act (Environment Canada 1993). Many articles that refer to arsenic toxicity do not distinguish between inorganic and organic derivatives. Arsenic toxicity is a function of the following: chemical form (arsenate organic metabolites are less toxic than inorganic forms); solubility (arsenite is more soluble and toxic than arsenate); valence state (arsenite is more toxic to the central nervous system than arsenate); dose; and duration of exposure (Yokel et al. 2006).

The valence state can affect the absorption, distribution, biotransformation, and elimination of metals and therefore their toxicity. In the case of inorganic arsenic, arsenate is excreted more rapidly than arsenite. Arsenite's higher retention and accumulation in vivo leads to its higher potential for toxicity compared to arsenate. The toxicity of arsenate appears to be related to its reduction to arsenite in vivo (Yokel et al. 2006). Inorganic arsenicals react with sulfhydryl (-SH) groups on cellular proteins resulting in inhibition of cellular oxidative pathways (e.g., oxidative phosphorylation).

Recent experimental data indicate trivalent arsenosugars are more toxic chronically than pentavalent arsenosugars in vitro (Andrewes et al. 2004). However, arsenosugars are generally not considered acutely toxic. Exceptions to these patterns in toxicity exist due to factors such as solubility, particle size, absorption rate and metabolism (Benedetti 1996; JECFA 1983). Overall, trivalent forms of arsenic are generally more toxic than pentavalent forms.

Currently, the best evidence characterizes arsenic metabolite toxicity as follows: MMA(III) > DMA (III) > As(III) > As(V) > MMA(V) > DMA(V) (Yokel et al. 2006). However, it is important to differentiate between organic arsenic metabolites and naturally-occurring organic arsenic compounds (e.g. arsenosugars, arsenobetaine). Organic arsenic metabolites are a result of detoxification processes, and are not the predominant form of arsenic present in seafood. In fact, Andrewes et al. (2004) found that both trivalent and pentavalent arsenosugars (found predominantly in seaweed) were significantly less toxic than MMA(III), DMA(III), or arsenate.

Chronic arsenic poisoning is a worldwide public health issue. Health effects associated with arsenic toxicity have been well documented, and include (but are not limited to) those listed in Table 1. Based on available information on toxicity of arsenic compounds, these health effects are assumed to result from exposure to inorganic arsenic compounds.

Table 1. Toxic effects of arsenic exposure.
(Sources: ATSDR 2005, 2006, 2007; Brown and Ross 2002; California Environmental Protection Agency 1996; WHO 2001)

Cancer	Arsenic is a known human carcinogen. Ingested inorganic arsenic is strongly associated with cancers of the skin, bladder, lung (and possibly other internal organs - kidney, liver, prostate).
Cardiovascular	Internal bleeding and heart inflammation (cardiomyopathy) may result from acute arsenic poisoning. Changes in blood vessels outside the heart and brain has resulted from chronic ingestion of arsenic in drinking water.
Gastrointestinal	Nausea may be experienced after acute and short-term arsenic ingestion. After short term exposure, initial gastrointestinal problems may lead to multi-organ failure may (including renal failure, respiratory failure, failure of vital cardiovascular and brain functions, and death).
Kidney effects	Renal failure may result from acute arsenic poisoning.

Liver	Oral exposure to inorganic arsenic may kill liver cells, elevating liver enzyme levels.
Neurological	Nervous system disorders (e.g. peripheral neuropathy) may result from damaged nerve cells. There are two documented cases of elevated urinary arsenic levels traced to kelp, where two women (aged 45 and 74 years) were admitted to hospital with neurological symptoms associated with ingestion of health food supplements prepared from kelp (Walkiw and Douglas 1974).
Pulmonary / Respiratory	Respiratory irritation resulting from inhalation. Lung cancer deaths among workers with chronic inhalation exposure to arsenic.
Reproductive	There are possible associations between arsenic exposure and spontaneous abortion and stillbirth, and congenital malformations (teratogenicity) in humans. Arsenic can cross the placental barrier in humans, potentially leading to arsenic accumulation in infant tissues. Teratogenicity of inorganic arsenic compounds has been reported in hamster, mouse, rat, and mouse, where sodium arsenate was teratogenic at doses 20 mg/kg. Animal studies also identified possible effects on conception and offspring growth and viability.
Hematologic	Bone marrow depression (i.e. an inability to make certain blood cells) may result from arsenic poisoning.
Skin	Changes in pigmentation (hyperpigmentation) and skin thickness on hands and feet (palmoplantar hyperkeratosis) are characteristic of chronic arsenic exposure. These changes may lead to malignant cancers.

Acute toxicity data have been collected on health effects of organic arsenic metabolite exposure in animals (rats, mice, and rabbits). Following oral exposure, no deaths were observed in mice administered arsenobetaine (dose not indicated). Common signs of toxicity of the organic arsenicals in mice included depression of motility and respiration, irritability, ataxia and convulsions. Death appeared to result from respiratory depression. For DMA and TMAO (trymethylarsine oxide), a period of increased spontaneous motility preceded the death of the mice (WHO 2001). Distribution and accumulation of arsenosugars in urine, blood, and wool of sheep fed a diet consisting almost entirely of seaweed was found to be similar to inorganic arsenic. Although no toxic effects were observed in sheep resulting from the diet, the study authors postulated that arsenosugars may be more toxic than previously thought due to their metabolic and accumulative properties (Andrewes et al. 2004).

3.6. Exposure

Environmental Sources

Humans may be exposed to inorganic and organic arsenic compounds via air, soil, food and water. Naturally-occurring concentrations vary around the world depending on history of land use and proximity to industrial areas. Exposure to volatile arsenicals in air represents a minor portion of the total intake from all sources. The primary route of exposure to arsenic for the

general population is dietary (i.e., food, water) (JECFA 1983, 1989; Vahter 1994). While food grown in soil with elevated levels may present an indirect route of exposure, most human arsenic exposure occurs from consumption of drinking water contaminated with inorganic arsenic. A review was conducted by Yoshida et al. (2004) for epidemiological studies on the dose–response relationships between inorganic arsenic exposure via the drinking water and chronic adverse health effects.

Exposure from Food and Water
Estimates of the daily dietary intake of total arsenic range from 1 to 1000 µg/day with a mean of 50.6 µg/day for females and 58.5 µg/day for males in the U.S. and an average of 38.1 µg/day in Canada. From 21-40% of the total dietary arsenic occurs in inorganic forms. Daily intake of inorganic arsenic ranges from 8.3 to 14 µg/day in the U.S. and from 4.8 to 12.7 µg/day in Canada. Intake from drinking water averages about 5 µg/day inorganic arsenic but can be much higher (10 to 100 µg/day) in geographical areas with high levels of arsenic in soil or groundwater (ATSDR 2007).

Dietary intake of arsenic is mainly attributable to consumption of grain, cereal, meats, poultry, seafood, and contaminated groundwater used for drinking. However marine foods (i.e. seafood) are the critical commodity, with reported arsenic levels of 0.39 - 42 ppm (Shils et al. 1999). Approximately 90% of arsenic in US diets comes from saltwater finfish and seafood (Borak and Hosgood 2007). However, the majority of arsenic in seafood is bound to complex organic compounds. The predominant organic species in marine organisms (fish, shrimp) is arsenobetaine, while marine algae (e.g. kelp) contain mainly arsenosugars. The results of in vitro experiments suggest that reduction of pentavalent arsenosugars to more toxic trivalent arsenosugars may occur in vivo and contribute to chronic toxicity of arsenic in humans who are exposed by eating seaweed (Andrewes et al. 2004), although seafood ingestion has not been linked to arsenic toxicity in humans or other mammals and human consumption of even large quantities of seafood results in an estimated margin of exposure of at least 10^3 to 10^4 less than the carcinogenic doses used in rodent studies (Borak and Hosgood 2007).

The proportion of toxic inorganic compounds found in seafood is generally very low; reported levels range from 1-3% of total arsenic in finfish, shrimp, fish and crustaceans (Donohue and Abernathy 1999; Schoof et al 1999a and 1999b). Thus, consumption of fish and seafood generally contributes very little to dietary intake of inorganic arsenic. While dietary inorganic arsenic intakes are estimated to range from <10 µg/day to 200 µg/day in various countries, it is important to note these values reflect different dietary patterns (individual and sub-populations) and variations in assumptions used in calculations. Sub-populations consuming large amounts of fish, such as Native peoples or fisherman and their families, may consume significantly more arsenic (primarily organic) per day. People who eat a lot of seafood (particularly fish, including shellfish and bottom-feeding fish) may consume in excess of 1000 µg organic arsenic (mainly arsenobetaine) per day, whereas daily intake of inorganic arsenic ranges from 10-20 µg in most countries (JECFA 1983 and 1989; Borak and Hosgood 2007; Foran et al. 2004; Vahter 1994).

In seaweeds, generally most of the arsenic is present as organic species as most algae have the ability to metabolically convert toxic inorganic arsenic into less toxic arsenosugars. Table 2 summarizes the concentrations of total arsenic compared to inorganic arsenic in some of the most

common edible seaweeds. Generally, green seaweeds (Phylum Chlorophyta) have the least total arsenic and are the lowest in inorganic arsenic, then the red seaweeds (Phylum Rhodophyta), with the brown seaweeds (Phylum Phaeophyta) having the highest total and inorganic arsenic levels (Almela et al. 2002, 2006). Table 2 shows that although there is a range of concentrations for any species as would be expected, different studies have provided comparable results.

Table 2. Arsenic content of edible seaweeds.

Edible Seaweed (type)	Total Arsenic (mg/kg dry wt)	Inorganic Arsenic (mg/kg dry wt)
Aonori, *Enteromorpha* sp. (green)	2.9±0.1[1], 2.3±0.1[3], 2.2[4]	0.59±0.02[1], 0.37±0.07[3], 0.35[4]
Sea lettuce, *Ulva lactuca* (green)	2.92-2.97[1], 2.99-3.17[3]	1.26-1.34[1], 1.27-1.37[3]
Dulse, *Palmaria palmata* (red)	7.56±0.02[3], 13[4]	0.44±0.06[3], 0.47-0.60[4]
Irish moss, *Chondrus crispus* (red)	12.7-16.1[4]	0.36-0.84[4]
Nori, *Porphyra* sp. (red)	33.8±2.9[1], 29[2], 23.7-30[3], 18.4-58.3[4], 18.2-31.9[5]	0.13±0.01[1], <0.3[2,5], 0.1-0.6[3,4]
Arame, *Eisenia bicyclis* (brown)	30[2], 24-30[3], 4.1-26.3[4], 27.9-32.3[5]	<0.3[2,5], 0.15-0.19[3], 0.14-1.4[4]
Bladderwrack, *Fucus* sp. (brown)	42.3-46.4[1], 50.0±0.3[3], 40[4]	1.22-1.29[1], 0.34±0.04[3], 0.29[4]
Hijiki, *Hizikia fusiforme* (brown)	99.4±4.0[1], 109[2], 115-141[3], 68-149[4], 94.6-134[5]	54.3±2.9[1], 77[2], 83-88[3], 42-117[4], 66.7-96.1[5]
Kombu, *Laminaria* sp. (brown)	28[2], 47-53[3], 40-116[4], 18.9-75.2[5]	<0.3[2,5], 0.25-0.30[3], 0.15-1.44[4]
Wakame, *Undaria pinnatifida* (brown)	36[2], 32-42[3], 28-46[4], 29.2-41.9[5]	<0.3[2,5], 0.15-0.26[3], 0.27-1.1[4]
Spirulina, *Spirulina platensis* (blue-green algae = Cyanobacteria)	0.23-0.71[4]	0.11-0.41[4]

[1]Laparra et al. 2003; [2]Rose et al. 2007; [3]Almela et al. 2002; [4]Almela et al. 2006; [5]Food Standards Agency 2004

An exception to the generally low level of inorganic arsenic in seafoods is hijiki seaweed (*Hizikia fusiforme* (Harvey) Okamura, Sargassaceae, Phylum Phaeophyta), which has much less ability to detoxify arsenic resulting in accumulation of both As(III) and As(V) inorganic forms. Hijiki has been found to contain levels as high as 117 mg/kg inorganic arsenic but may average 77 mg/kg, while most other species of marine algae had concentrations of 0.4 mg/kg or less (Almela et al. 2002, 2006; Laparra et al. 2003; Rose et al. 2007). While the percentage of inorganic out of the total arsenic decreased from 73% in raw material to 67% in prepared hijiki to 55% when soaked for use (Rose et al. 2007), bioaccessibility (maximum soluble concentration in the gastrointestinal medium) of the inorganic arsenic increased significantly after cooking (Laparra et al. 2003).

Among people who eat seaweeds, an average consumption is estimated to be 3 g/day for nori, 7 g/day for kombu, 10 g/day for wakame, 14 g/day for arame, and 12-25 g/day for hijiki (Almela et al. 2002, Rose et al. 2007). With respect to hijiki, this level of exposure to inorganic arsenic is sufficient to present a risk to health (Rose et al. 2007, CFIA 2001).

Although recent evidence suggests that the proportion of inorganic arsenic in foods is higher than was previously assumed (Yost et al. 1998), current literature indicates that arsenic levels in foods are as variable as is shown for algae in Table 2. Furthermore, Hughes (2006) notes that estimating inorganic arsenic exposure through measurement of total urinary arsenic (a common biomarker of exposure) may be confounded by consumption of seafood with high concentrations of organic arsenic. Additional research is needed to characterize the precision of measurement of arsenic exposure in humans (Pellizzari and Clayton 2006), and bioavailability of dietary inorganic and organic arsenic species taking into account common methods of preparation (Laparra et al. 2003; Food Standards Agency 2004; Rose et al. 2007).

Exposure from Therapeutic Products

Historically, arsenic is almost synonymous with "poison" although it has been used as a therapeutic agent for more than 2,400 years. Introduction of arsenic as a therapeutic drug into modern medicine is generally attributed to the work of Thomas Fowler in the late 1700s. Fowler's solution of 1% arsenic trioxide (7.6 g arsenite/L) gained popularity as a therapeutic agent for a variety of ailments in the late 1800s (e.g., skin diseases, asthma, periodic fevers, and pain). Arsenic triiodide was used as part of a combination therapy for sarcoma (Gaston 1897). Inorganic arsenic preparations were later used to treat leukemia, psoriasis, and chronic bronchial asthma. Although pharmacological uses for inorganic arsenic generally have been replaced with more effective alternatives, arsenic trioxide was approved by the US FDA in 2000 for the treatment of relapsed or refractory acute promyelocytic leukemia since it has been found to be effective with only limited side effects in many of the 20% to 30% of patients not responding to all-trans retinoic acid and combination chemotherapy (Antman 2001).

Organic arsenic antibiotics were extensively used in the early 20th century primarily in the treatment of microbial diseases. The most famous of these were the arsphenamine derivatives Salvarsan, released in 1910, and subsequently the less toxic Neosalvarsan, for the treatment of syphilis and yaws. Salvarsan was one of the first chemotherapeutic agents ever developed to successfully treat infectious diseases (Gensini et al. 2007). Carbarsone was marketed for the treatment of amoebic infections but by the 1980s, therapeutic preparations of organic arsenic were mostly phased out of use in humans (Shils et al. 1999; NRC 1999; ATSDR 2006; IPCS 1981).

Some Asian proprietary medicines that are manufactured in China, Hong Kong, and other Asian countries have been reported to contain levels of inorganic arsenic ranging from 25 μg/g (ppm) to 107,000 μg/g (Chan 1994 in ATSDR 2007). Of 54 samples of Asian medicines purchased in Vietnam, Hong Kong, and health food and Asian groceries stores in Florida, New York and New Jersey, four contained daily doses of arsenic exceeding 0.1 mg, of which one provided a daily dose of 7.4 mg and another contained 16 mg of arsenic (Garvey et al. 2001 in ATSDR 2007). A survey of the heavy metal content of 70 Ayurvedic herbal medicine products manufactured in South Asia and found in Boston-area stores found 6 that contained arsenic, with a median concentration of 430 μg/g; range, 37 to 8130 μg/g (Saper et al. 2004).

Fifty medicinally important leafy herbs contained arsenic in concentrations ranging from 0.12 to 7.36 μg/g, with a mean of 2.38 ± 1.2 μg/g (Reddy and Reddy 1997 in ATSDR 2007). Arsenic concentrations ranged from 0.005 to 3.77 μg/g in 95 dietary supplements purchased from retail

stores in the Washington, DC, area in 1999 (Dolan et al. in ATSDR 2007). Arsenic concentrations in selected herbal medicines commercially available in the United States were as follows: Valerian 0.0016 to 0.0085 µg/g, St. John's Wort 0.0065 to 0.0178 µg/g, Passionflower 0.0024 to 0.0124 µg/g, and Echinacea 0.0021 to 0.0102 µg/g (Huggett et al. 2001 in ATSDR 2007).

There are dilute homeopathic medicines with market authorization from Health Canada that contain arsenic trioxide (arsenicum album) or arsenic triiodide (arsenicum iodatum) (Health Canada 2007b, 2008). The Homoeopathic Pharmacopoeia of the United States sets out maximum concentrations for OTC sale: arsenic trioxide 6X (1 ppm), arsenic tribromide 6X, arsenic triiodide 6X, metallic arsenic 8X (0.01 ppm), arsenic trisulfide red or yellow forms 6X (HPCUS 2004). Arsenic toxicity has been reported in India from homeopathic medicines that were not sufficiently dilute, such as Arsenic Bromide 1X and Arsenicum Sulfuratum Flavum 1X (Chakraborti et al. 2003; Prasad et al. 2006); arsenic has been detected in homeopathic medicines at concentrations up to 650 ppm (ATSDR 2007).

An additional potential source of arsenic is as a contaminant in kelp-containing natural health products or dietary supplements. Various types of kelp (such as Bladderwrack and Laminaria) are used for a variety of ailments, including thyroid disorders, iodine deficiency, constipation obesity, and arthritis (ATSDR 2006; Gursche and Rona 1997; Jellin 2008a, b). Doses for Laminaria supplements are typically 500-650 mg/day (Jellin 2008b). A case report was recently published suggesting the potential for arsenic toxicity from long-term use of herbal kelp supplements containing elevated quantities of arsenic at a dosage providing 82 mg/day of *Laminaria digitata* (Amster et al. 2001). However, analytical results for the kelp supplement did not distinguish between inorganic and organic arsenic, and there were other issues with the analysis of the evidence in the case report (Fabricant 2007; Lewis 2007; McGuffin and Dentali 2007). For bladderwrack capsules the dosage typically ranges from 200-600 mg/day (Kerbel and Foppa 2008).

Quality controls and their regulatory enforcement are potentially useful to minimize the risk from arsenic in kelp or other products. For example, the European Pharmacopoeia (EDQM 2004) has a monograph for kelp (*Fucus vesiculosus* L., *F. serratus* L. or *Ascophyllum nodosum* Le Jolis) that sets out a maximum tolerance for total arsenic of 90 ppm; a specification for inorganic vs. organic forms would be even better.

Exposure and Arsenic Speciation

Speciation can be defined as the occurrence of an element in different physical states, where the state affects the route and extent of exposure, uptake/absorption, and toxicodynamics (Yokel et al. 2006). Arsenic speciation in terrestrial plants can be influenced by arsenic species present in the soil; ability of the plant to take up arsenic; ability of the plant to synthesize arsenic species; and the presence of arsenic species adsorbed to plant root surfaces (Meharg and Hartley-Whitaker 2002). Recent evidence indicates that plants preferentially accumulate organic arsenic compounds in regenerative parts, whereas inorganic arsenic species are present mainly in the roots and aerial biomass (Szakova et al. 2006).

Bioavailability can be defined as the rate and extent that a chemical can be absorbed by a living organism. While there is general consensus that toxicity and bioavailability of arsenic varies with the arsenic species, extensive research has been directed towards assessing toxicity and risk associated with total concentrations which may not be reflective of arsenic speciation in biota and environmental samples. For example, a food (e.g. seafood) may have high total concentration exceeding guidelines, but most of the arsenic is likely in the non-toxic organic form. Overall it appears contamination of water with arsenic is likely more harmful to humans than arsenic in food due to higher bioavailability in drinking water. In addition, it is important to consider the contribution of arsenic species and their respective bioavailability when estimating exposure risk (Akter et al. 2005).

Health effects associated with exposure to inorganic arsenic via the oral route are more likely to result from drinking water contaminated with arsenic than from food. Consequently, it is reasonable to consider naturally occurring organic arsenic compounds separately from inorganic compounds. However, identifying the form (species) of arsenic occurring in environmental media is still a recent development. For the purposes of estimating population exposure, it is generally assumed that most of the arsenic in air, water, and soil is inorganic and that the majority of arsenic in plant and animal matrices is organic (IPCS 1981, 1983; Schoof et al. 1998).

3.7. Current Limits of Exposure

The following standards have been established by regulatory agencies worldwide (Table 3):

Table 3. International Standards and Guidelines for Arsenic

Country	Regulatory Body	Standard/ Guideline	Studies / Toxicological data	Reference
Canada	Natural Health Products Directorate (NHPD), Health Canada	tolerance limit for total arsenic as contaminant in NHPs: **0.14 µg/kg bw/day**	NSF contaminant limit of 0.01 mg/day divided by 70 kg DRI standard adult reference weight	Health Canada 2007a; NSF 2006
Canada	Health Canada Federal-Provincial-Territorial Committee on Drinking Water	tolerance limit of **0.3 µg/L**	Based on a level that would present an "essentially negligible" level of risk, i.e. upper 95% confidence interval for lifetime cancer risk of 1.9 $x10^{-6}$ to 1.39 x 10^{-5}	Health Canada 2006
United States	Environmental Protection Agency (EPA)	toxicological reference dose (RfD) for arsenic: **0.3 µg/kg per day**	Survey of 40,000 Taiwanese residents; based on a NOAEL of 0.8 µg/kg per day and an Uncertainty Factor of 3X	Shils et al. 1999; IRIS 1998

Table 3. International Standards and Guidelines for Arsenic				
Country	**Regulatory Body**	**Standard/ Guideline**	**Studies / Toxicological data**	**Reference**
United States	Environmental Protection Agency (EPA)	revised maximum contaminant level (MCL) for total arsenic in drinking water: **10 µg/L** (previously 50 µg/L)	Not indicated.	Shils et al. 1999; EPA 2001; Benedetti 1996
United States	Environmental Protection Agency (EPA)	toxicological reference doses (RfD) for organic arsenical pesticides: **100 µg/kg** (MMA, acute) **120 µg/kg** (DMA, acute) **30 µg/kg per day** (MMA, chronic) **14 µg/kg per day** (DMA, chronic)	MMA (acute): NOAEL = 10 mg/kg/day, UF = 100X DMA acute): NOAEL = 12 mg/kg/day, UF = 100X MMA (chronic): NOAEL = 3.2 mg/kg/day, UF = 100X DMA (chronic): BMDL= 0.43 mg/kg/day, UF = 30X	EPA 2006
United States	US Agency for Toxic Substances and Disease Registry (ATSDR)	minimum risk levels (MRLs) for oral exposure to inorganic arsenic: **5 µg/kg per day** (acute) **0.3 µg/kg per day** (chronic)	oral acute (≤14 days): based on gastrointestinal effects, and a UF/SF of 10X oral chronic (≥365 days): based on dermal sensitivity and a UF/SF of 3X	ATSDR 2007
International	Joint Expert Committee of the FAO/WHO on Food Additives (JECFA)	provisional tolerable daily intake (PTDI) for ingested inorganic arsenic: **2.1 µg/kg bw/day** provisional tolerable weekly intake (PTWI) for ingested inorganic arsenic: **15 µg/kg bw/week**	Not indicated	JECFA 1983, 1989 Benedetti 1996

Based on assessment of the available evidence, the US National Research Council (NRC) Subcommittee on Arsenic in Drinking Water decided that the current EPA MCL for arsenic in drinking water of 50 µg/L (0.05 mg/L) did not meet the EPA's goal for protecting public health and recommended that the level be revised downwards (National Research Council 1999).

JECFA (1983; 1989) indicated there is insufficient data available to estimate a TDI for organic arsenic in food, and recognized a lack of the following information: (1) arsenic accumulation in humans exposed to various forms of arsenic in food and drinking water; (2) animal studies investigating identification, absorption, elimination and toxicity of arsenic compounds in food; (3) contribution of arsenic in fish to human body burden of arsenic; and (4) epidemiological studies on populations exposed to elevated levels of naturally-occurring arsenic of known speciation in drinking water and marine products.

Inorganic Arsenic Tolerance Limit

The most recent and thorough review of arsenic toxicity (ATSDR 2007) has made the following estimates of exposure levels posing minimal risk to humans (MRLs) for arsenic. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (non-carcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on non-cancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

An MRL of 0.005 mg As/kg/day has been derived for acute-duration (14 days or less) oral exposure to inorganic arsenic. The MRL of 0.005 mg As/kg/day was calculated by applying an uncertainty factor of 10 (10 for use of a lowest-observed-adverse-effect level (LOAEL) and 1 for human variability) to the LOAEL of 0.05 mg As/kg/day. An MRL of 0.0003 mg As/kg/day has been derived for chronic-duration (365 days or more) oral exposure to inorganic arsenic. The MRL was derived by applying an uncertainty factor of 3 (for human variability) to the NOAEL of 0.0008 mg/kg/day.

Table 4. Comparison of FAO/WHO PTDI and ATSDR MRL for Chronic Exposure to Inorganic Arsenic

DRI Lifestage (IOM 2006)	Reference Weight (kg)	i-As FAO/WHO PTDI (µg/kg bw/d)	i-As FAO/WHO PTDI (µg/d)	i-As ATSDR Chronic MRL (µg/kg/bw/d)	i-As ATSDR Chronic MRL (µg/d)
Infants 2-6 mo	6	2.10	12.60	0.30	1.80
Infants 7-12 mo	9	2.10	18.90	0.30	2.70
Toddlers 1-3 y	12	2.10	25.20	0.30	3.60
Early Childhood 4-8 y	20	2.10	42.00	0.30	6.00
Puberty: Males 9-13 y	36	2.10	75.60	0.30	10.80
Puberty: Females 9-13 y	37	2.10	77.70	0.30	11.10
Adolescent Females 14-18 y	54	2.10	113.40	0.30	16.20
Adult Females 19-30 y	57	2.10	119.70	0.30	17.10
Adult Females 31-50 y	57	2.10	119.70	0.30	17.10
Adult Females 51-70 y	57	2.10	119.70	0.30	17.10
Adult Females 70+ y	57	2.10	119.70	0.30	17.10
Adolescent Males 14-18 y	61	2.10	128.10	0.30	18.30

Adult Males 19-30 y	70	2.10	147.00	0.30	21.00
Adult Males 31-50 y	70	2.10	147.00	0.30	21.00
Adult Males 51-70 y	70	2.10	147.00	0.30	21.00
Adult Males 70+ y	70	2.10	147.00	0.30	21.00
Pregnancy					
Up to 18 y	54	2.10	113.40	0.30	16.20
19-50 y	57	2.10	119.70	0.30	17.10
Lactation/Breastfeeding					
Up to 18 y	54	2.10	113.40	0.30	16.20
19-50 y	57	2.10	119.70	0.30	17.10

Comparing the calculated Minimal Risk Levels (ATSDR 2007) from Table 4 to the daily dietary intake of inorganic arsenic that ranges from 8.3 to 14 µg/day in the U.S. and from 4.8 to 12.7 µg/day in Canada, it would appear that our diet supplies approximately 50% of the amount of arsenic that our body can tolerate without significant risk to health. Therefore, a conservative approach to the tolerance limit for inorganic arsenic in natural health products or dietary supplements is warranted. If we propose to divide the MRL by 10 to set a tolerance limit for supplements of 0.03 µg/kg body weight/day inorganic arsenic, which would be reasonable from a safety perspective, would it be practicable? Table 5 provides Tolerable Daily Intake values for the different DRI (IOM 2006) life stages for inorganic arsenic using 10% of the chronic MRL.

Table 5. 10% of ATSDR MRL for Chronic Exposure to Inorganic Arsenic

DRI Lifestage (IOM 2006)	Reference Weight (kg)	i-As ATSDR Chronic MRL 10% (µg/kg bw/day)	i-As TDI (µg/day)
Infants 2-6 mo	6	0.03	0.18
Infants 7-12 mo	9	0.03	0.27
Toddlers 1-3 y	12	0.03	0.36
Early Childhood 4-8 y	20	0.03	0.60
Puberty: Males 9-13 y	36	0.03	1.08
Puberty: Females 9-13 y	37	0.03	1.11
Adolescent Females 14-18 y	54	0.03	1.62
Adult Females 19-30 y	57	0.03	1.71
Adult Females 31-50 y	57	0.03	1.71
Adult Females 51-70 y	57	0.03	1.71
Adult Females 70+ y	57	0.03	1.71
Adolescent Males 14-18 y	61	0.03	1.83
Adult Males 19-30 y	70	0.03	2.10
Adult Males 31-50 y	70	0.03	2.10
Adult Males 51-70 y	70	0.03	2.10

Adult Males 70+ y	70	0.03	2.10
Pregnancy			
Up to 18 y	54	0.03	1.62
19-50 y	57	0.03	1.71
Lactation/Breastfeeding			
Up to 18 y	54	0.03	1.62
19-50 y	57	0.03	1.71

Comparing the calculated TDI from Table 5 of approximately 2 µg/day with the fact that a selection of important medicinal herbs were found to contain a mean arsenic concentration of 2 µg/g (Reddy and Reddy 1997 in ATSDR 2007) and that commercial preparation processes may reduce that concentration by 100x to 1000x (Huggett et al. 2001 in ATSDR 2007), it appears that a tolerance limit of 0.03 µg/kg body weight/day inorganic arsenic would be met by the majority of natural health products on the North American market, with the possible exception of some Asian medicines which have already been determined to present health risks from excessive arsenic content.

Organic Arsenic Tolerance Limit

ATSDR (2007) has derived a chronic-duration oral MRL of 0.01 mg MMA/kg/day for MMA based on a 95% lower confidence limit on the benchmark dose ($BMDL_{10}$) of 1.09 mg MMA/kg/day for increased incidence of progressive nephropathy in male mice exposed to MMA in the diet for 2 years and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). ATSDR has derived a chronic-duration oral MRL of 0.02 mg DMA/kg/day for DMA based on a $BMDL_{10}$ of 1.80 mg DMA/kg/day for increased vacuolization of the urothelium in the urinary bladder of female mice exposed to DMA in the diet for 2 years and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR (2007) has not derived any MRLs for the specific organic arsenic derivatives found naturally occurring in seafood or algal supplements due to the lack of suitable data.

In the absence of a specific chronic MRL for the organic arsenic derivatives commonly found in NHPs, and understanding that they are much less toxic than inorganic arsenic but not necessarily completely innocuous, it is worthwhile to consider a conservative yet practical provisional approach to setting a tolerance limit for organic arsenic derivatives. If one assumes the extreme case that 100% of the arsenosugars and arsenolipids might be metabolized to DMA, which is the major metabolite, one might consider the chronic MRL for DMA of 20 µg/kg bw/day to be a reasonable provisional tolerance limit for organic arsenic.

Total Arsenic Tolerance Limit

The current NHPD tolerance limit for total arsenic in natural health products is 0.14 µg/kg body weight/day. This was derived by taking the NSF-International Standard for Dietary Supplements (NSF 2006) contamination limit for finished products of 0.01 mg/day and dividing that by the 70 kg standard adult male reference weight (IOM 2006). This very conservative limit for total arsenic daily intake from NHPs is less than half of the most recent and conservative ATSDR (2007) chronic MRL for inorganic arsenic of 0.3 µg/kg bw/day and just 7% of the JECFA (1989)

provisional TDI of 2.0 µg/kg bw/day (15 µg/kg bw/week) for chronic exposure to inorganic arsenic. In the context that most of the daily intake of arsenic is likely to be from dietary (food and water) rather than supplement sources and that most of the risk is associated with inorganic arsenic, the current tolerance limit for total arsenic appears to provide adequate mitigation of any risk to health.

Appendix 1 provides tables of calculations of the worst-case scenarios for the two most common marine algal NHPs, *Laminaria* and *Fucus*, demonstrating that at the highest levels of total and inorganic arsenic reported in the literature, at a commonly recommended maximum dose, these products would consistently fail a total arsenic test but would pass an arsenic speciation test with separate tolerance limits for inorganic arsenic and organic arsenic as suggested above, except in children, for whom these products are not generally recommended in any case.

4. OPTIONS ANALYSIS

The Options Analysis takes into consideration the following points:

- The 0.14 µg/kg bw/day total arsenic tolerance limit is based on information for inorganic arsenic;
- Levels of inorganic arsenic in foods are generally low relative to organic arsenic compounds;
- Inorganic arsenic compounds are more toxic than organic arsenic compounds, therefore the majority of the health risk from intake of arsenic in food is likely due to presence of inorganic arsenic;
- Regulation of total (inorganic) arsenic levels in food products are expected to be protective of the Canadian population;
- There are no MRLs for the organic arsenic derivatives such as arsenosugars and arsenolipids found naturally occurring in algal and seafood supplements due to the lack of suitable data;
- DMA is the major metabolite of arsenosugars and arsenolipids.

Option #1:
Maintain the current tolerance limit of 0.14 µg/kg bw/day for total arsenic in NHPs, which takes into account dosage and subpopulation, with no distinction between inorganic and organic arsenic.

Pro:

- Status quo;
- Simple, inexpensive, readily available testing protocols and service labs.

Con:

- The status quo results in rejection of certain marine NHPs because testing indicates they have excessive levels of arsenic when in fact the risk to health is minimal.

Option #2:
As a first approach, maintain the current tolerance limit of 0.14 µg/kg bw/day for total arsenic in NHPs, but if the total arsenic level in a particular NHP is found to exceed the tolerance limit taking into account dosage and subpopulation, the market authorization holder may undertake additional testing with arsenic speciation to demonstrate that the level of inorganic arsenic consumed by ingesting the product would be <0.03µg/kg bw/day and the level of organic arsenic consumed by ingesting the product would be <20 µg/kg bw/day.

Pro:
- There is no additional testing requirement or cost for the majority of NHPs which are compliant with the total arsenic tolerance limit;
- For those few products that do exceed the limit due to a higher content of organic arsenic, testing for arsenic using a speciation approach allows market authorization holders to demonstrate that the risk to health is minimal because both the inorganic and the organic arsenic derivatives are within the tolerances;
- Real life evidence of arsenic contamination in seaweeds was used to verify that this approach is practical.

Con:
- At this time arsenic speciation analysis is likely to be expensive and not readily available; with limited demand this is unlikely to change.

5. RECOMMENDATION

The NHPD recommends Option 2.

6. DECISION

Constructive criticism of the document and support for NHPD's recommendation of Option 2 was kindly provided by Health Canada's Marketed Health Products Directorate, the Health Products and Food Branch Inspectorate. The United States Pharmacopoeia provided advice on additional methodologies which have been incorporated into this version of the IAS. Option 2 was accepted by the NHPD Expert Advisory Committee on March 4, 2008.

7. IMPLEMENTATION

NHPD recommends either the use of HPLC coupled with ICP-MS or ICP-AES or the Food Chemicals Codex method for analysis of inorganic and organic arsenic compounds in finished natural health products. Testing methods for arsenic speciation should be provided if an applicant/company decides to distinguish levels of organic and inorganic arsenic in the product. In this case, a quality assessment will be conducted by NHPD to determine whether the chosen test methods are acceptable and whether the product adheres to the NHPD quality standard.

Section 2.4.3.2 (Chemical Contaminants) of the NHPD publication Evidence for Quality of Finished Natural Health Products (Health Canada 2007) will be revised to reflect the decision.

Health Canada's Health Products and Food Branch Inspectorate and Food Directorate have both purchased new equipment in order to have the ability to analyse for organic versus inorganic arsenic levels. While the equipment is not yet operational, this is an initiative in progress.

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APPENDIX 1. DEMONSTRATION CALCULATIONS

Total Arsenic Tolerable Daily Intake (TDI) Calculator

Product Name: **Fucus, worst case scenario**

DRI Lifestage	Reference Weight (kg)	t-As NHPD Tolerance Limit (ug/kg bw/d)	t-As TDI (ug/d)	Enter Value: [t-As] (ug/g dry wt)	Enter Value: Daily Dose (g)	Calculated Daily Intake (ug/d)	Intake vs. TDI: TDI Exceeded or Not
Infants 2-6 mo	6	0.14	0.84	50.30	0.60	30.18	Yes
Infants 7-12 mo	9	0.14	1.26	50.30	0.60	30.18	Yes
Toddlers 1-3 y	12	0.14	1.68	50.30	0.60	30.18	Yes
Early Childhood 4-8 y	20	0.14	2.80	50.30	0.60	30.18	Yes
Puberty: Males 9-13 y	36	0.14	5.04	50.30	0.60	30.18	Yes
Puberty: Females 9-13 y	37	0.14	5.18	50.30	0.60	30.18	Yes
Adolescent Females 14-18 y	54	0.14	7.56	50.30	0.60	30.18	Yes
Adult Females 19-30 y	57	0.14	7.98	50.30	0.60	30.18	Yes
Adult Females 31-50 y	57	0.14	7.98	50.30	0.60	30.18	Yes
Adult Females 51-70 y	57	0.14	7.98	50.30	0.60	30.18	Yes
Adult Females 70+ y	57	0.14	7.98	50.30	0.60	30.18	Yes
Adolescent Males 14-18 y	61	0.14	8.54	50.30	0.60	30.18	Yes
Adult Males 19-30 y	70	0.14	9.80	50.30	0.60	30.18	Yes
Adult Males 31-50 y	70	0.14	9.80	50.30	0.60	30.18	Yes
Adult Males 51-70 y	70	0.14	9.80	50.30	0.60	30.18	Yes
Adult Males 70+ y	70	0.14	9.80	50.30	0.60	30.18	Yes
Pregnancy							
Up to 18 y	54	0.14	7.56	50.30	0.60	30.18	Yes
19-50 y	57	0.14	7.98	50.30	0.60	30.18	Yes
Lactation/Breastfeeding							
Up to 18 y	54	0.14	7.56	50.30	0.60	30.18	Yes
19-50 y	57	0.14	7.98	50.30	0.60	30.18	Yes

Inorganic Arsenic Tolerable Daily Intake (TDI) Calculator

Product Name: **Fucus, worst case scenario**

DRI Lifestage	Reference Weight (kg)	i-As ATSDR Chronic MRL 10% (ug/kg bw/d)	i-As TDI (ug/d)	Enter Value: [i-As] (ug/g dry wt)	Enter Value: Daily Dose (g)	Calculated Daily Intake (ug/d)	Intake vs. TDI: TDI Exceeded or Not
Infants 2-6 mo	6	0.03	0.18	1.29	0.60	0.77	Yes
Infants 7-12 mo	9	0.03	0.27	1.29	0.60	0.77	Yes
Toddlers 1-3 y	12	0.03	0.36	1.29	0.60	0.77	Yes
Early Childhood 4-8 y	20	0.03	0.60	1.29	0.60	0.77	Yes
Puberty: Males 9-13 y	36	0.03	1.08	1.29	0.60	0.77	No
Puberty: Females 9-13 y	37	0.03	1.11	1.29	0.60	0.77	No
Adolescent Females 14-18 y	54	0.03	1.62	1.29	0.60	0.77	No
Adult Females 19-30 y	57	0.03	1.71	1.29	0.60	0.77	No
Adult Females 31-50 y	57	0.03	1.71	1.29	0.60	0.77	No
Adult Females 51-70 y	57	0.03	1.71	1.29	0.60	0.77	No
Adult Females 70+ y	57	0.03	1.71	1.29	0.60	0.77	No
Adolescent Males 14-18 y	61	0.03	1.83	1.29	0.60	0.77	No
Adult Males 19-30 y	70	0.03	2.10	1.29	0.60	0.77	No
Adult Males 31-50 y	70	0.03	2.10	1.29	0.60	0.77	No
Adult Males 51-70 y	70	0.03	2.10	1.29	0.60	0.77	No
Adult Males 70+ y	70	0.03	2.10	1.29	0.60	0.77	No
Pregnancy							
Up to 18 y	54	0.03	1.62	1.29	0.60	0.77	No
19-50 y	57	0.03	1.71	1.29	0.60	0.77	No
Lactation/Breastfeeding							
Up to 18 y	54	0.03	1.62	1.29	0.60	0.77	No
19-50 y	57	0.03	1.71	1.29	0.60	0.77	No

Organic Arsenic Tolerable Daily Intake (TDI) Calculator

Product Name: **Fucus, worst case scenario**

DRI Lifestage	Reference Weight (kg)	o-As Reference Dose (ug/kg bw/d)	o-As TDI (ug/d)	Enter Value: [o-As] (ug/g dry wt)	Enter Value: Daily Dose (g)	Calculated Daily Intake (ug/d)	Intake vs. TDI: TDI Exceeded or Not
Infants 2-6 mo	6	20.00	120.00	49.01	0.60	29.41	No
Infants 7-12 mo	9	20.00	180.00	49.01	0.60	29.41	No
Toddlers 1-3 y	12	20.00	240.00	49.01	0.60	29.41	No
Early Childhood 4-8 y	20	20.00	400.00	49.01	0.60	29.41	No
Puberty: Males 9-13 y	36	20.00	720.00	49.01	0.60	29.41	No
Puberty: Females 9-13 y	37	20.00	740.00	49.01	0.60	29.41	No
Adolescent Females 14-18 y	54	20.00	1080.00	49.01	0.60	29.41	No
Adult Females 19-30 y	57	20.00	1140.00	49.01	0.60	29.41	No
Adult Females 31-50 y	57	20.00	1140.00	49.01	0.60	29.41	No
Adult Females 51-70 y	57	20.00	1140.00	49.01	0.60	29.41	No
Adult Females 70+ y	57	20.00	1140.00	49.01	0.60	29.41	No
Adolescent Males 14-18 y	61	20.00	1220.00	49.01	0.60	29.41	No
Adult Males 19-30 y	70	20.00	1400.00	49.01	0.60	29.41	No
Adult Males 31-50 y	70	20.00	1400.00	49.01	0.60	29.41	No
Adult Males 51-70 y	70	20.00	1400.00	49.01	0.60	29.41	No
Adult Males 70+ y	70	20.00	1400.00	49.01	0.60	29.41	No
Pregnancy							
Up to 18 y	54	20.00	1080.00	49.01	0.60	29.41	No
19-50 y	57	20.00	1140.00	49.01	0.60	29.41	No
Lactation/Breastfeeding							
Up to 18 y	54	20.00	1080.00	49.01	0.60	29.41	No
19-50 y	57	20.00	1140.00	49.01	0.60	29.41	No

Inorganic Arsenic Tolerable Daily Intake (TDI) Calculator

Product Name: **Laminaria, worst case scenario**

DRI Lifestage	Reference Weight (kg)	i-As ATSDR Chronic MRL 10% (ug/kg bw/d)	i-As TDI (ug/d)	Enter Value: [i-As] (ug/g dry wt)	Enter Value: Daily Dose (g)	Calculated Daily Intake (ug/d)	Intake vs. TDI: TDI Exceeded or Not
Infants 2-6 mo	6	0.03	0.18	1.44	0.65	0.94	Yes
Infants 7-12 mo	9	0.03	0.27	1.44	0.65	0.94	Yes
Toddlers 1-3 y	12	0.03	0.36	1.44	0.65	0.94	Yes
Early Childhood 4-8 y	20	0.03	0.60	1.44	0.65	0.94	Yes
Puberty: Males 9-13 y	36	0.03	1.08	1.44	0.65	0.94	No
Puberty: Females 9-13 y	37	0.03	1.11	1.44	0.65	0.94	No
Adolescent Females 14-18 y	54	0.03	1.62	1.44	0.65	0.94	No
Adult Females 19-30 y	57	0.03	1.71	1.44	0.65	0.94	No
Adult Females 31-50 y	57	0.03	1.71	1.44	0.65	0.94	No
Adult Females 51-70 y	57	0.03	1.71	1.44	0.65	0.94	No
Adult Females 70+ y	57	0.03	1.71	1.44	0.65	0.94	No
Adolescent Males 14-18 y	61	0.03	1.83	1.44	0.65	0.94	No
Adult Males 19-30 y	70	0.03	2.10	1.44	0.65	0.94	No
Adult Males 31-50 y	70	0.03	2.10	1.44	0.65	0.94	No
Adult Males 51-70 y	70	0.03	2.10	1.44	0.65	0.94	No
Adult Males 70+ y	70	0.03	2.10	1.44	0.65	0.94	No
Pregnancy							
Up to 18 y	54	0.03	1.62	1.44	0.65	0.94	No
19-50 y	57	0.03	1.71	1.44	0.65	0.94	No
Lactation/Breastfeeding							
Up to 18 y	54	0.03	1.62	1.44	0.65	0.94	No
19-50 y	57	0.03	1.71	1.44	0.65	0.94	No

Total Arsenic Tolerable Daily Intake (TDI) Calculator

Product Name: **Laminaria, worst case scenario**

DRI Lifestage	Reference Weight (kg)	t-As NHPD Tolerance Limit (ug/kg bw/d)	t-As TDI (ug/d)	Enter Value: [t-As] (ug/g dry wt)	Enter Value: Daily Dose (g)	Calculated Daily Intake (ug/d)	Intake vs. TDI: TDI Exceeded or Not
Infants 2-6 mo	6	0.14	0.84	116.00	0.65	75.40	Yes
Infants 7-12 mo	9	0.14	1.26	116.00	0.65	75.40	Yes
Toddlers 1-3 y	12	0.14	1.68	116.00	0.65	75.40	Yes
Early Childhood 4-8 y	20	0.14	2.80	116.00	0.65	75.40	Yes
Puberty: Males 9-13 y	36	0.14	5.04	116.00	0.65	75.40	Yes
Puberty: Females 9-13 y	37	0.14	5.18	116.00	0.65	75.40	Yes
Adolescent Females 14-18 y	54	0.14	7.56	116.00	0.65	75.40	Yes
Adult Females 19-30 y	57	0.14	7.98	116.00	0.65	75.40	Yes
Adult Females 31-50 y	57	0.14	7.98	116.00	0.65	75.40	Yes
Adult Females 51-70 y	57	0.14	7.98	116.00	0.65	75.40	Yes
Adult Females 70+ y	57	0.14	7.98	116.00	0.65	75.40	Yes
Adolescent Males 14-18 y	61	0.14	8.54	116.00	0.65	75.40	Yes
Adult Males 19-30 y	70	0.14	9.80	116.00	0.65	75.40	Yes
Adult Males 31-50 y	70	0.14	9.80	116.00	0.65	75.40	Yes
Adult Males 51-70 y	70	0.14	9.80	116.00	0.65	75.40	Yes
Adult Males 70+ y	70	0.14	9.80	116.00	0.65	75.40	Yes
Pregnancy							
Up to 18 y	54	0.14	7.56	116.00	0.65	75.40	Yes
19-50 y	57	0.14	7.98	116.00	0.65	75.40	Yes
Lactation/Breastfeeding							
Up to 18 y	54	0.14	7.56	116.00	0.65	75.40	Yes
19-50 y	57	0.14	7.98	116.00	0.65	75.40	Yes

Inorganic Arsenic Tolerable Daily Intake (TDI) Calculator

Product Name: **Laminaria, worst case scenario**

DRI Lifestage	Reference Weight (kg)	i-As ATSDR Chronic MRL 10% (ug/kg bw/d)	i-As TDI (ug/d)	**Enter Value:** [i-As] (ug/g dry wt)	**Enter Value:** Daily Dose (g)	**Calculated** Daily Intake (ug/d)	**Intake vs. TDI:** TDI Exceeded or Not
Infants 2-6 mo	6	0.03	0.18	1.44	0.65	0.94	Yes
Infants 7-12 mo	9	0.03	0.27	1.44	0.65	0.94	Yes
Toddlers 1-3 y	12	0.03	0.36	1.44	0.65	0.94	Yes
Early Childhood 4-8 y	20	0.03	0.60	1.44	0.65	0.94	Yes
Puberty: Males 9-13 y	36	0.03	1.08	1.44	0.65	0.94	No
Puberty: Females 9-13 y	37	0.03	1.11	1.44	0.65	0.94	No
Adolescent Females 14-18 y	54	0.03	1.62	1.44	0.65	0.94	No
Adult Females 19-30 y	57	0.03	1.71	1.44	0.65	0.94	No
Adult Females 31-50 y	57	0.03	1.71	1.44	0.65	0.94	No
Adult Females 51-70 y	57	0.03	1.71	1.44	0.65	0.94	No
Adult Females 70+ y	57	0.03	1.71	1.44	0.65	0.94	No
Adolescent Males 14-18 y	61	0.03	1.83	1.44	0.65	0.94	No
Adult Males 19-30 y	70	0.03	2.10	1.44	0.65	0.94	No
Adult Males 31-50 y	70	0.03	2.10	1.44	0.65	0.94	No
Adult Males 51-70 y	70	0.03	2.10	1.44	0.65	0.94	No
Adult Males 70+ y	70	0.03	2.10	1.44	0.65	0.94	No
Pregnancy							
Up to 18 y	54	0.03	1.62	1.44	0.65	0.94	No
19-50 y	57	0.03	1.71	1.44	0.65	0.94	No
Lactation/Breastfeeding							
Up to 18 y	54	0.03	1.62	1.44	0.65	0.94	No
19-50 y	57	0.03	1.71	1.44	0.65	0.94	No

Organic Arsenic Tolerable Daily Intake (TDI) Calculator

Product Name: **Laminaria, worst case scenario**

DRI Lifestage	Reference Weight (kg)	o-As Reference Dose (ug/kg bw/d)	o-As TDI (ug/d)	**Enter Value:** [o-As] (ug/g dry wt)	**Enter Value:** Daily Dose (g)	**Calculated** Daily Intake (ug/d)	**Intake vs. TDI:** TDI Exceeded or Not
Infants 2-6 mo	6	20.00	120.00	114.56	0.65	74.46	No
Infants 7-12 mo	9	20.00	180.00	114.56	0.65	74.46	No
Toddlers 1-3 y	12	20.00	240.00	114.56	0.65	74.46	No
Early Childhood 4-8 y	20	20.00	400.00	114.56	0.65	74.46	No
Puberty: Males 9-13 y	36	20.00	720.00	114.56	0.65	74.46	No
Puberty: Females 9-13 y	37	20.00	740.00	114.56	0.65	74.46	No
Adolescent Females 14-18 y	54	20.00	1080.00	114.56	0.65	74.46	No
Adult Females 19-30 y	57	20.00	1140.00	114.56	0.65	74.46	No
Adult Females 31-50 y	57	20.00	1140.00	114.56	0.65	74.46	No
Adult Females 51-70 y	57	20.00	1140.00	114.56	0.65	74.46	No
Adult Females 70+ y	57	20.00	1140.00	114.56	0.65	74.46	No
Adolescent Males 14-18 y	61	20.00	1220.00	114.56	0.65	74.46	No
Adult Males 19-30 y	70	20.00	1400.00	114.56	0.65	74.46	No
Adult Males 31-50 y	70	20.00	1400.00	114.56	0.65	74.46	No
Adult Males 51-70 y	70	20.00	1400.00	114.56	0.65	74.46	No
Adult Males 70+ y	70	20.00	1400.00	114.56	0.65	74.46	No
Pregnancy							
Up to 18 y	54	20.00	1080.00	114.56	0.65	74.46	No
19-50 y	57	20.00	1140.00	114.56	0.65	74.46	No
Lactation/Breastfeeding							
Up to 18 y	54	20.00	1080.00	114.56	0.65	74.46	No
19-50 y	57	20.00	1140.00	114.56	0.65	74.46	No

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Signature of Submitter * Kerri L. Levanseler Date 5-07-08

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Please insert a check (X) in the appropriate place to indicate if you wish the item to be considered as an action item or as an information item.

Action _____X_____ Information _____

NSF Standard(s) Impacted**: 173**

Issue Statement:
Provide a concise statement of the issue, which reference as appropriate any specific section(s) of the standard(s) that are related to the issue.

To update the method reference used in Standard 173 for aristolochic acids.

Background:
Provide a brief background statement indicating the cause and nature of concern, the impacts identified relevant to public health, public understanding, etc, and any other reason why the issue should be considered by the Committee.

Standard 173 currently recommends testing for Aristolochic Acid using the US FDA Method. This method was modified, optimized and fully validated. This is now an AOAC Official Method; method 2007.05.

Recommendation:
If action by the Joint Committee is being requested, clearly state what action is needed: e.g., recommended changes to the standard(s) including the current text of the relevant section(s) indicating deletions by use of ~~strike-out~~ and additions by highlighting or underlining; e.g., reference of the issue to a Task Force for detailed consideration; etc. If recommended text changes are more than a half page, please attach a separate document.

Recommend the standard be updated as follows…

7.4 Test methods for chemical contaminants

Testing shall be performed based on ~~USFDA's Method for Determination of Aristolochic Acid in Traditional Chinese Medicines and Dietary Supplements~~ AOAC Official Method 2007.05, Aristolochic Acid I in Botanicals and Dietary Supplements Potentially Contaminated with Aristolochic Acid I (LC-UV with Confirmation by LC/MS).

Supplementary Materials (photographs, diagrams, reports, etc.):
If not provided electronically, the submitter will be responsible to have sufficient copies to distribute to committee members.

NA

Submitter _Kerri L. Levanseler Date __05-01-08

Item No. DS-2008-4
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Signature of Submitter * Angie Ewing Date 5-14-08

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Action ____X_____ Information _____

NSF Standard(s) Impacted**:**

NSF/ANSI 173

Issue Statement:

Provide a concise statement of the issue, which reference as appropriate any specific section(s) of the standard(s) that are related to the issue.

Diethylene glycol (DEG) is a suspected contaminant of glycerin. FDA is recommending that pharmaceutical manufacturers screen for diethylene glycol contamination in glycerin supplies. Glycerin is also used as an excipient in dietary supplements.

This issue was previously submitted in 2007 (DS-2007-7). The method referenced has since been updated per the recommendation of the JC in 2007.

Background:

Provide a brief background statement indicating the cause and nature of concern, the impacts identified relevant to public health, public understanding, etc, and any other reason why the issue should be considered by the Committee.

There have been repeated instances of DEG poisoning in Haiti, Argentina, Bangladesh, India, Nigeria and Panama. The cause of the poisoning was from DEG-contaminated glycerin in acetaminophen syrup. It was determined that pharmaceutical manufacturers did not perform testing on the glycerin sources but relied on certificates of analysis provided by the supplier.

Recommendation:

If action by the Joint Committee is being requested, clearly state what action is needed: e.g., recommended changes to the standard(s) including the current text of the relevant section(s) indicating deletions by use of ~~strike-out~~ and additions by highlighting or underlining; e.g., reference of the issue to a Task Force for detailed consideration; etc. If recommended text changes are more than a half page, please attach a separate document.

NSF is recommending a diethylene glycol contaminant testing requirement for any dietary supplement that contains glycerin in the formulation.

Supplementary Materials (photographs, diagrams, reports, etc.):

If not provided electronically, the submitter will be responsible to have sufficient copies to distribute to committee members.

Addition as of 5-14-08: The methods to be utilized has been added to the proposed revised Standard Language (see attached).

Submitter __Angie Ewing_____ Date __5-14-08___

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5.3 Contaminants

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5.3.4 Natural toxins

Botanicals listed in annex A shall not contain aristolochic acid (limit of detection is 0.5 μg/gm).

5.3.5 Known adulterants

Products shall be evaluated to ensure that they do not contain known adulterants including, but not limited to, the following:

- *Eleutherococcus senticosus* shall not contain *Periploca sepium* root.
- *Plantago lanceolata* shall not contain *Digitalis lanata* leaf.
- *Scutellaria lateriflora* shall not contain *Teucrium chamaedrys*.
- *Stephania tetranda* shall not contain *Aristolochia fangchi*.

5.3.6 Industrial Contaminants

For ingredients and products containing natural fish oil, manufacturers shall have controls in place to screen for polychlorinated biphenyls (PCBs), polychlorinated dibenzo-para-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and dioxin-like PCBs in the oil ingredient.

The content of dioxins and furans expressed as the sum of PCDDs and PCDFs shall not exceed 2 pg WHO-TEQ per gram of oil, dioxin-like PCBs shall not exceed 3 pg WHO-TEQ per gram of oil, and total PCBs shall not exceed 0.09 mg/kg of oil (w/w).[1] Total PCBs shall include IUPAC congeners 28, 52, 101, 118, 138, 153, and 180.

Ingredients and products containing glycerin shall be tested for diethylene glycol contamination. Diethylene glycol shall not exceed 0.1%.

5.3.~~6~~7 Other product claims

Claims that a product is free of a particular contaminant or substance shall be verified in accordance with 7.4 and/or 8.

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7.4 Test methods for chemical contaminants

Testing shall be performed based on USFDA's Method for Determination of Aristolochic Acid in Traditional Chinese Medicines and Dietary Supplements.

The most appropriate method shall be used to confirm claims for the product under evaluation. The source of these methods may include AOAC International, USP, EPA, FDA, AHP, European, German, Japanese monographs, INA, industry standards, etc. The use of any new method shall require that a validation be performed which includes an evaluation of specificity, linearity, reproducibility, spike

[1] Council for Responsible Nutrition, Omega 3 Fatty Acids Voluntary Monograph, March 2006.

recovery, and method detection limit. More rigorous validation could follow according to the guidelines of ICH, FDA, CEN, GLP, and/or AOAC, as appropriate.

Unless a manufacturer has controls in place to assess the rancidity of oil ingredients, the following testing shall be performed. The Peroxide Value of the oil shall be tested according to AOAC Method 965.33 (which is equivalent to AOCS 8-53). The p-Anisidine Value of the oil shall be tested by AOCS Cd 18-90.[7] The Totox Number shall be calculated as the sum of the p-Anisidine Value and two times the Peroxide Value.

7.5 Test methods for industrial contaminants

Testing of fish oil samples for PCBs and dioxin-like PCBs shall be performed utilizing a slightly modified high resolution gas chromatography-high resolution mass spectrometry (HRGC-HRMS) method, EPA Method 1668, Revision A: Chlorinated Biphenyl Congeners in Water, Soil Sediment and Tissue by HRGC-HRMS. Testing of fish oil samples for dioxins and furans shall be performed utilizing a slightly modified high resolution gas chromatography-high resolution mass spectrometry (HRGC-HRMS) method, EPA Method 1613, Revision B: Tetra- through Octa-Chlorinated Dioxins and Furans by Isotope Dilution HRGC-HRMS.

Manufacturers shall meet this testing requirement by one of the following routes;

- through the use of compliant ingredients as demonstrated by third party testing;
- performing testing utilizing a laboratory accredited for PCBs, Dioxin and Furans under ISO 17025 and providing the sample results, data, and quality control results, for review to support compliance; or
- having testing performed by an accredited testing laboratory.

Testing for diethylene glycol in finished products containing glycerin shall be performed utilizing liquid chromatography mass spectrometry (LC-MS) methodology, which has been shown to be valid for the particular sample matrix being tested. Alternately, the glycerin raw material itself may be tested utilizing gas chromatography as described in the glycerin monograph USP 31-NF 26.

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Signature of Submitter * Kerri L. Levanseler Date 5-01-08

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Action ___X_____ Information ____ _____

NSF Standard(s) Impacted**: 173**

Issue Statement:
Provide a concise statement of the issue, which reference as appropriate any specific section(s) of the standard(s) that are related to the issue.

To update the Normative References section.

Background:
Provide a brief background statement indicating the cause and nature of concern, the impacts identified relevant to public health, public understanding, etc, and any other reason why the issue should be considered by the Committee.

This issue is to be balloted with the changes to Tables 3 and 4 as it contains some normative reference updates coinciding with those changes.

Recommendation:
If action by the Joint Committee is being requested, clearly state what action is needed: e.g., recommended changes to the standard(s) including the current text of the relevant section(s) indicating deletions by use of ~~strike-out~~ and additions by highlighting or underlining; e.g., reference of the issue to a Task Force for detailed consideration; etc. If recommended text changes are more than a half page, please attach a separate document.

Additions/deletions to the Normative References (see attached).

Supplementary Materials (photographs, diagrams, reports, etc.):
If not provided electronically, the submitter will be responsible to have sufficient copies to distribute to committee members.
NA

Submitter _Kerri L. Levanseler Date __05-09-08

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2 Normative references

The following documents contain provisions that, through reference in this text, constitute provisions of this Standard. At the time this Standard was written, the editions indicated were valid. All documents are subject to revision, and parties are encouraged to investigate the possibility of applying the most recent edition of the document indicated below.

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Ashwagandha Root*, April 2000[1]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Astragalus Root*, August 1999[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Bilberry fruit*, 2001[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Black Cohosh root*, 2002[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Black Haw Bark*, June 2000[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Chaste Tree Fruit*, 2001[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Cramp Bark*, February 2000[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Cranberry*, 2002[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Dang Gui Root*, 2003[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Echinacea purpurea Root*, 2004[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Ginkgo Leaf*, 2003[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Goldenseal*, 2001[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Hawthorn Berry*, June 1999[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Hawthorn Leaf with Flower*, February 1999[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Reishi Mushroom*, September 2000[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *St. John's Wort*, July 1997[4]

[1] American Herbal Pharmacopoeia, P. O. Box 66809, Scotts Valley, CA 95067

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Schisandra Berry*, October 1999[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Valerian Root*, April 1999[4]

AHP, American Herbal Pharmacopoeia and Therapeutic Compendium, *Willow Bark*, December 1999[4]

AHPA, American Herbal Products Association, *Herbs of Commerce*, 2nd Edition, 2000[2]
AOAC International, Food and Drug Administration, *Bacteriological Analytical Manual*, eighth edition (1998)[3]

AOAC International, *AOAC Guidelines for Single Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals*[6]

AOAC International, *Official Methods of Analysis*, 18th edition (2005)[6]

AOCS, American Oil Chemists Society International, *Sampling and Analysis of Commercial Fats and Oils*, Cd 18-90 (1997)[4]

BHP, British Herbal Medicine Association, *British Herbal Pharmacopoeia*, 1996[5]

Code of Federal Regulations, Title 40, (40 CFR) Part 141, *National Primary Drinking Water Regulations*[6]

Code of Federal Regulations, Title 21, Chapter 29, *Federal Food, Drug, and Cosmetic Act*[9]

Compliance Services International, *Analytical Method for the Determination of Quintozene and Its Degradates and Impurities in Ground Dried Ginseng Root by Gas Chromatography* Laboratory validation of analytical method number CSI-023-01, 1999[7]

Council for Responsible Nutrition, Omega 3 Fatty Acids Voluntary Monograph, March 2006

Dietary Supplements Health and Education Act of 1994, (an amendment to the Federal Food, Drug and Cosmetic Act): Public Law 103-417 – October 25, 1994[8]

~~INA, *Allicin by High-Performance Liquid Chromatography*[9]~~

INA, *Black Cohosh Assay by ELSD*[12]

INA, *Catechins and Gallic Acid in Green Tea by HPLC*[12]

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[2] American Herbal Products Association, 8484 Georgia Ave., Suite 370, Silver Spring, MD 20910

[3] AOAC International, 481 Frederick Avenue, Suite 500, Gaithersburg, MD 20877

[4] AOCS, 2211 W. Bradley Ave., Champaign, IL 61821

[5] British Herbal Medicine Association, P. O. Box 304, Bournemouth, Dorset, BH7 6JZ, England

[6] U. S. Government Printing Office, Washington, D. C. 20402

[7] Compliance Services International, 1112 Alexander Avenue, Tacoma, WA 98421

[8] Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20401

[9] Institute for Nutraceutical Advancement (INA), c/o NSF International, 789 Dixboro Road, Ann Arbor, MI 48105

~~INA, *Fatty Acid Content in Saw Palmetto by Gas Chromatography*[12]~~

~~INA, *Ginkgo Flavonol Glycoside Assay by HPLC*[12]~~

INA, *Ginkgoterpenoid Assay by HPLC*[12]

~~INA, *Kavalactone Assay by HPLC*[12]~~

~~INA, *Phenolics in Echinacea by HPLC*[12]~~

INA, *St. John's Wort Assay by HPLC*[12]

~~INA, *Sterols Content in Saw Palmetto by Gas Chromatography*[12]~~

International Code for Botanical Nomenclature (St. Louis Code), 2000[10]

NTIS/IEC 17025: 1999 *General requirements for the competence of testing and calibration laboratories*[11]

The Merck Index: *An Encyclopedia of Chemicals, Drugs and Biologicals* (Annual) [12]

NSF International White Book of NSF Registered and USDA Authorized Proprietary Substances and Nonfood Compounds[13]

Public Health Security and Bioterrorism Preparedness and Response Act of 2002, 42 USC 201[9]

USEPA, *Determination Of Dissolved Hexavalent Chromium In Drinking Water, Groundwater And Industrial Wastewater Effluents By Ion Chromatography*, EPA Method 218.6, Revision 3.3 – August 1991.[14]

USEPA *Methods for the Determination of Metals in Environmental Samples – Supplement*, 1 – EPA/600/R-94-111 – May 1994[14]

USEPA *Microwave Assisted Acid Digestion of Sediments, Sludges, Soils and Oils*, EPA Method 3510 – September 1994[14]

USEPA *National Primary Drinking Water Regulations* (40 CFR part 141) [14]

USFDA, *Bacteriological Analytical Manual,* eighth edition, 2001[18]

[10] Sixteenth International Botanical Congress, St. Louis, Missouri, July-August 1999. Publ. 2000, Koeltz Scientific Books

[11] National Technical Information Service, 5285 Port Royal Rd., Springfield, VA 22161

[12] Merck & Company, One Merck Drive, Whitehouse Station, NJ 08889

[13] NSF International, 789 North Dixboro Road, Ann Arbor, MI 48105

[14] USEPA, Office of Water, Washington, D. C. 20460

USFDA *Dietary Supplement and Nonprescription Drug Consumer Protection Act*[18]

USFDA *Food Allergen Labeling and Consumer Protection Act of 2004*[18]

USFDA, *Pesticide Analytical Manual,* Volume 1. Multiresidue Methods [Base Manual 3rd Edition] 1994 – NTIS report number PB9294911899[15]

USFDA, *Pesticide Analytical Manual,* Volume 1 Updates. Irregular reports. 2003 – NTIS report number PB2003911800[18]

USFDA, *Pesticide Analytical Manual,* Volume 2. Methods for Individual Residues [Base Manual] – 1991 NTIS report number PB92911999[18]

USFDA, *Food Code 2001 Recommendations of the United States Public Health Service Food and Drug Administration,* NTIS report number PB2002100819[18]

USFDA, *A Multi-Residue Pesticide Monitoring Procedure for the Determination of 112 Halogenated Pesticides Using Gas Chromatography with Mass Selective Detection and Selected ion Monitoring.* LIB # 4304[18]

USFDA, *Determination of Aristolochic Acid in Traditional Chinese Medicines and Dietary Supplements*[16]

USP, United States Pharmacopeia, USP ~~29~~31-NF ~~24~~26 (or most current version)[17]

WHO, *World Health Organization Monographs on Selected Medicinal Plants*, Volume 1, 2 and 3[18]

WHO, *Guidelines for Drinking-Water Quality*[21]

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5.4 Disintegration

5.4.1. Uncoated, film-coated, plain-coated, and hard and soft gelatin capsules

Supplements shall be verified as meeting the requirements for disintegration when tested using the methods described in the most current version of USP-NF ~~USP 28 NF 23~~ and in the USP monograph if applicable to the product being evaluated. For products where no USP monograph applies, testing will be performed using deionized water as the immersion fluid for a time period of 60 min.

5.4.2. Delayed release (enteric coated tablets)

Supplements which are claimed to be “delayed release” or “enteric coated” shall be verified as meeting the disintegration requirements for delayed release (enteric coated tablets) using the

[15] U. S. Department of Commerce, Technology Administration, National Technical Information Services, 5285 Port Royal Road, Springfield, Virginia 22161

[16] USFDA Forensic Chemistry Center, 1141 Central Pky, Cincinnati, OH 45202

[17] United States Pharmacopeia, 121601 Twinbrook Parkway, Rockville, MD 20852-1790

[18] World Health Organization, 1211 Geneva 27, Switzerland

method described in the most current version of USP ~~28~~ NF ~~23~~. The method employs simulated gastric fluid for one hour, followed by simulated gastric fluid for a time period no greater than 8 h or for the time specified in the USP monograph if applicable to the product being evaluated.

5.4.3. Timed or slow release

Supplements which claim "timed release" or "slow release" shall be tested for disintegration using the method described in the most current version of USP ~~28~~ NF ~~23~~. Testing will be performed using 0.1 M hydrochloric acid as the immersion fluid for a time period no greater than 8 h or for the time period indicated on the product label. The tablets shall not disintegrate within the first hour of immersion.

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6.1.2 Vitamins

The identity of vitamins shall be evaluated in accordance with the methods listed in the most current ~~year~~ version of USP ~~29~~ NF ~~24~~. If no method exists or if improved technology allows for a more accurate and precise method to be developed, one may be developed. The use of any new method shall require that a validation be performed, following the principles of the AOAC Single Lab Validation Guideline[23] as a minimum, which includes an evaluation of specificity and reproducibility. More rigorous validation could follow according to the guidelines of ICH[19], USFDA[20], GLP[21], CEN[22], and/or AOAC[23], as appropriate.

6.1.3 Minerals

The identity of minerals shall be evaluated in accordance with the methods listed in the most current version of USP ~~29~~ NF ~~24~~. If no method exists or if improved technology allows for a more accurate and precise method to be developed, one may be developed. The use of any new method shall require that a validation be performed, following the principles of the AOAC Single Lab Validation Guideline[23] as a minimum, which includes an evaluation of specificity and reproducibility. More rigorous validation could follow according to the guidelines of ICH[24], USFDA[25], GLP[26], CEN[27], and/or AOAC[23], as appropriate.

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[19] ICH Secretariat, c/o IFPMA, 15, chemin Louis-Dumant, P.O. Box 195, 1211 Geneva 20, Switzerland

[20] US Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857

[21] US Food and Drug Administration, Office of Regulatory Affairs, 5600 Fishers Lane, Rockville, MD 20857

[22] European Committee for Standardization (CEN), 36 Rue de Stassart, B-1050 Brussels