

Dietary Supplement- Standard 173
Metal Contaminant Acceptance Levels
NSF International
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TABLE OF CONTENTS

INTRODUCTION	1
2.0 ARSENIC	2
2.1 REGULATORY STATUS	2
2.1.1 USEPA	2
2.1.2 USFDA	3
2.1.3 World Health Organization	3
2.1.4 California Proposition 65	3
2.3 Determination of acceptable limits for finished products.	4
2.4 Determination of acceptable limits for raw materials.	4
3.0 CADMIUM	5
3.1 REGULATORY STATUS	5
3.1.1 USEPA	5
3.1.2 USFDA	5
3.1.3 WHO	5
3.1.4 California Proposition 65	6
3.1.5 Other Regulatory Values	6
3.2 Estimation of Maximum Daily Intake	6
3.3 Determination of acceptable limits for finished products.	7
3.4 Determination of acceptable limits for raw materials.	8
4.0 CHROMIUM (VI)	8
4.1 REGULATORY STATUS	8
4.1.1 USEPA	8
4.1.2 USFDA	8
4.1.3 California Proposition 65	8
4.1.4 Other Regulatory Values	8
4.2 Estimation of Maximum Daily Intake	9
4.3 Determination of acceptable limits for finished products.	9
4.4 Determination of acceptable limits for raw materials.	9
5.0 LEAD	10
5.1 REGULATORY STATUS	10
5.1.1 USEPA	10
5.1.1.1 USEPA IRIS Substance File	10
5.1.1.2 USEPA MCLG	10
5.1.1.3 USEPA Action Level	10
5.1.2 USFDA	11
5.1.3 World Health Organization	11
5.1.4 California Proposition 65	12
5.1.5 Other Regulatory Values	12
CDC	12
OSHA	12
5.2 Estimation of Maximum Daily Intake	12
5.3 Determination of acceptable limits for finished products.	14
5.4 Determination of acceptable limits for raw materials.	14
6.0 MERCURY	14
6.1 REGULATORY STATUS	14
6.1.1 USEPA	15
6.1.2 USFDA	16
6.1.3 World Health Organization	16
6.1.4 California Proposition 65	17
6.2 Estimation of Maximum Daily Intake	17
6.3 Determination of acceptable limits for finished products.	18
6.4 Determination of acceptable limits for raw materials.	18
7.0 REFERENCES	19

INTRODUCTION

This document has been prepared to support the selection of acceptable contaminant levels for arsenic, cadmium, chromium (VI), lead and mercury when products are tested to NSF Standard 173, Dietary Supplements. Raw materials and finished products are tested to determine the level of undeclared metals and their acceptance is based on the levels determined in this document.

In order to make this determination, NSF considered the current USEPA, Health Canada and Australia/New Zealand regulatory values for the metals, as well as other regulatory values and guidelines including those set by the food and Agricultural Organization (FAO), World Health Organization (WHO), USFDA, ATSDR (Minimal Risk Levels), European Agency for the Evaluation of Medicinal Products, International Pharmacopoeia, Expanded Commission E Monographs, United States Pharmacopoeia, European Pharmacopoeia American Herbal Pharmacopoeia, British Pharmacopoeia and California EPA Proposition 65.

The general guidelines for the risk assessments performed by NSF included those from the National Research Council (1983) and from The Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a, 1997b). Other guidelines used in the development of this assessment may have included the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), (new) Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998a), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), Health Effects Testing Guidelines (OPPTS series 870, U.S. EPA 1998b; U.S. EPA 40 CFR Part 798, 1997b) and the World Health Organization's International Programme on Chemical Safety Environmental Health criteria series, including Environmental Health Criteria 210 -Principles for the Assessment of Risks to Human Health from Exposure to Chemicals (IPCS 1999).

The risk assessments were based on toxicological data and endpoints as well as human dietary intake and exposure data. The basis of the calculations for the acceptable levels of the metals in the finished product follows a mathematical model, as published by FAO/WHO, in which an acceptable (or tolerable) daily intake in mg/kg body weight is multiplied by the average body mass of an adult (60 kg). Based on the best available science, and ultimately the need to depend on safety considerations, a ten percent default allocation of the relative source contribution of the daily intake to dietary supplements was incorporated as a safety factor. It was considered by FAO/WHO that it was not acceptable if 30% or more of the acceptable daily intake of a particular heavy metal derived from food or drinking water or both was accounted for by the additional consumption of dietary supplements. A 1% allocation of the ADI to account for the relative source contribution of dietary supplements as a component of daily food intake was advocated but it is NSF's judgment that a 10% source contribution factor would not significantly increase the daily concentration or health risk. Accordingly, the 10% allocation was used in this document. The formula is therefore given by

Acceptable Level =

Acceptable daily intake (mg/kg body weight per day) x adult body mass (kg) x 10%

For raw materials, where existing information from respected sources such as the British Herbal Pharmacopoeia and the WHO Monographs on selected medicinal plants: on acceptable levels in raw materials was not available, the following mathematical model was employed where the acceptable level in raw materials is given by:

Acceptable Level =

$$\frac{\text{Acceptable daily intake (mg/kg body weight per day) x adult body mass (kg) x extraction factor}}{\text{Average daily dose of dietary supplement x 100 (safety factor)}}$$

2.0 ARSENIC

2.1 REGULATORY STATUS

Because humans are exposed to multiple forms of inorganic arsenic in occupational and non-occupational settings, inorganic arsenic is regulated in the workplace, as well as food and water. Inorganic arsenic is an element that can exist in several forms, most commonly arsenite (As^{+3}) and arsenate (As^{+5}).

2.1.1. USEPA

As part of the USEPA IRIS toxicological review of arsenic, an oral RfD of 0.0003 mg/kg-day for inorganic arsenic was developed, based on a NOAEL of 0.0008 mg/kg-day in humans and an uncertainty factor of three (U.S. EPA, 1998c). The critical effect for the RfD derivation was hyper pigmentation, keratosis, and vascular complications reported after human oral exposure to food and water containing arsenic (Tseng, 1977; Tseng et al., 1968). The uncertainty factor of three was selected to account for the lack of data to preclude reproductive toxicity as a critical effect and to account for uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals. The USEPA IRIS toxicological review for arsenic also includes a carcinogenicity assessment that is based upon the 1986 U.S. EPA cancer risk assessment guidelines (USEPA, 1998c). The USEPA concluded that sufficient evidence exists to conclude that arsenic is a human carcinogen, based upon increased lung cancer mortality in humans, increased internal organ cancers in humans (liver, kidney, lung, and bladder), and an increased incidence of skin cancer in humans (USEPA, 1998c). The U.S. EPA derived an oral slope factor (q_1^*) of 1.5 (mg/kg/Day) for arsenic using epidemiological data reported by Tseng et al. (1968) and Tseng (1977), using a time- and dose-related formulation of the linearized multistage model. In 1997, an expert panel convened by the U.S. EPA concluded that arsenic was likely a human carcinogen via the oral and inhalation routes, and that the dose-response curve for arsenic at low doses would likely be nonlinear (USEPA, 1998d).

2.1.2 USFDA

The USFDA regulates arsenic in food under the authority of the Federal Food, Drug, and Cosmetic Act (FFDCA). Arsenic is an essential trace element in multiple animal species, including chickens, rats, swine, and goats (Uthus, 1992). As such, it is added to animal feed. To control levels of arsenic in animal tissues, the USFDA established tolerances for total residues of combined arsenic in various edible tissues of swine, as well as edible tissues and eggs of chickens and turkeys (21 CFR §556.60), at concentrations listed below:

- A maximum of 2 mg arsenic/kg uncooked liver or kidney of swine;
- A maximum of 0.5 mg arsenic/kg uncooked muscle tissue or by-products other than liver and kidney in swine;
- A maximum of 0.5 mg arsenic/kg uncooked muscle tissue in chickens and turkeys;
- A maximum of 2 mg arsenic/kg uncooked edible by-products in chickens or turkeys; and
- A maximum of 0.5 mg arsenic/kg eggs from chickens or turkeys.

The USFDA regulates the concentration of arsenic in bottled water. Currently, the USFDA allows a maximum level of 50 µg/L of arsenic in bottled water (21 CFR §165.110). This level will be reduced to 10 µg/L.

2.1.3 World Health Organization

In 1981, WHO evaluated the data available for arsenic (JECFA 1982). They considered that the most important toxicological data are derived from studies of human exposure to drinking-water and that the available epidemiological evidence allowed a tentative conclusion that arsenicism could be associated with water supplies containing an upper arsenic concentration of 1 mg/l or greater, and concentration of 0.1 mg/l may give rise to presumptive signs of toxicity. Assuming a daily water consumption of 1.5 litres, JECFA estimated that 1.5 mg/day of inorganic arsenic are likely to result in chronic arsenic toxicity and daily intakes of 0.15 mg may also be toxic in the long term to some individuals. On the basis of the data available, JECFA were able to provide an estimate of 0.002 mg/kg body weight as a provisional maximum tolerable daily intake for ingested inorganic arsenic; no figure could be arrived at for organic arsenicals in food.

In 1988 the Joint FAO/WHO Expert Committee on Food Additives (JECFA 1989) confirmed the previous evaluation made in 1981 by assigning a Provisional Maximum Tolerable weekly intake (PTWI) for inorganic arsenic of 0.015 mg/kg body weight with the clear understanding that the margin between the PTWI and intakes reported to have toxic effects in epidemiological studies was narrow.

2.1.4 California Proposition 65

Proposition 65 is the common name for *California's Safe Drinking Water and Toxic Enforcement Act of 1986*. Among other requirements, Proposition 65 requires the Governor of California to publish a list of chemicals that are known to the State of California to cause cancer, birth defects, or other reproductive harm. Arsenic is listed under Proposition 65 as a carcinogen, and has been assigned No-Significant-Risk-Levels (NSRLs) of 0.06 µg/day (for inhalation exposures) and 10 µg/day (for routes of exposure other than inhalation). As defined by the California Environmental Protection Agency, a No-Significant-Risk-Level represents a daily

intake level calculated to result in a cancer risk not to exceed one excess case of cancer in 100,000 individuals exposed over a 70-year lifetime (Cal/EPA, 1994). Arsenic is also listed under Proposition 65 as a developmental toxicant, but has not been assigned an Acceptable Intake Level (AIL) for developmental effects (Cal/EPA, 1996).

2.3 Determination of acceptable limits for finished products.

The derivation of an acceptable limit for finished products was based on the Joint FAO/WHO Expert Committee on Food Additives Provisional Maximum Tolerable weekly intake (PTWI) for inorganic arsenic of 0.015 mg/kg body weight. A calculated tolerable daily intake would be $0.015/7 = 0.02$ mg/kg body weight. Assuming a 60 kg adult, this would result in a tolerable daily intake of 0.13 mg inorganic arsenic.

With a 10% allocation to dietary supplements an acceptable limit for finished products containing arsenic would be 0.01 (rounded) mg/day

The JECFA PTWI was chosen to derive the acceptable limit as WHO had performed a comprehensive risk assessment on arsenic. They took into account different chemical and toxicological characteristics of the various molecular species and oxidation states occurring in food. It is necessary to distinguish between the species in order to present a full picture of the content of arsenic in food and what impact the intake of arsenic in food can have on the consumer. The most toxic forms of arsenic in food and water are the inorganic arsenic (III) and (V).

Both WHO and USEPA used epidemiological data based on inorganic arsenic in drinking water to derive their values. An assessment of the organic arsenic species in food could not be established by WHO due to the lack of toxicological data. It was considered that WHO had a more comprehensive data set with respect to human intake for arsenic via the diet and drinking water. They combined that with the data on human food consumption from around the world in their effort to derive a meaningful estimate of intake using toxicological standards. Therefore it was appropriate to use their data to derive an acceptable limit for dietary supplements as finished products.

2.4 Determination of acceptable limits for raw materials.

The acceptable limit for arsenic in raw materials was taken from the British Herbal Pharmacopoeia and is 5 ppm.

3.0 CADMIUM

3.1 REGULATORY STATUS

3.1.1 USEPA

EPA has developed reference doses for cadmium in water and food (USEPA 1985). The reference doses were based on data from multiple studies of both humans and animals using the highest level of cadmium found in the human renal cortex not associated with significant proteinuria. The EPA set a reference dose of 0.001 mg/kg/day for food using a NOAEL of 0.01 mg/kg/day and an uncertainty factor of 10. Their action level for cadmium was based on the assumption that one-quarter of the total cadmium absorbed may come from water. In 1989 the EPA's MCL and MCLG for cadmium was changed from 0.010 mg/kg to 0.005 mg/kg to agree with WHO's and NAS's drinking water guideline for cadmium (54 FR 22062).

3.1.2 USFDA

The U.S. FDA has approved cadmium under the following conformances:

- (21 CFR 73.1646 – 1647, Listing of color additives exempt from certification) FDA has set a level of 15 ppm for the amount of cadmium that can be used in bronze powder, copper powder, and zinc oxide used for color additives.
- (21 CFR 103.35) FDA set a level of 0.005 mg/L of cadmium allowed in bottle water.
- (21 CFR 172.399) FDA set a level of 0.05 ppm for amount of cadmium allowable in zinc methionine sulfate tablets.
- (CPG 7117.06) FDA set action levels of 0.5 ug/mL, 0.5 ug/mL and 0.25 ug/mL for the amount of cadmium leaching from ceramic flatware, small hollowware, and large hollowware, respectively.

3.1.3 WHO

Cadmium was evaluated by JECFA at its sixteenth, thirty-third, and forty-first meetings. At its sixteenth meeting, the Committee allocated a provisional tolerable weekly intake (PTWI) of 400–500 µg of cadmium per person. At its thirty-third meeting, the Committee retained this PTWI but expressed it in terms of intake per kilogram of body weight (7 µg/kg body weight). In 1992, the International Programme on Chemical Safety published a monograph on cadmium which provided a detailed review of the available information on the health effects of cadmium and a description of the models on which the PTWI was based (WHO, 1992). At its forty-first meeting, in 2000, the Committee used the monograph as the basis for its evaluation and retained the PTWI of 7 µg/kg body weight (JECFA 2000).

3.1.4 California Proposition 65

Proposition 65 is the common name for *California's Safe Drinking Water and Toxic Enforcement Act of 1986*. Among other requirements, Proposition 65 requires the Governor of California to publish a list of chemicals that are known to the State of California to cause cancer, birth defects, or other reproductive harm. Proposition 65 has set a level of 0.05 ug/day for cadmium for inhalation exposure. Currently, there is not a level set for oral exposure.

3.1.5 Other Regulatory Values

The Agency for Toxic Substances and Disease Registry (ATSDR) set a minimum risk level (MRL) for cadmium at 0.0002 mg/kg/day based on a chronic oral study using renal dysfunction as an endpoint and an uncertainty factor of 10.

3.2 Estimation of Maximum Daily Intake

Inhalation, dermal contact and ingestion are the primary routes of human exposure to cadmium and cadmium compounds (ATSDR, 1997). While dietary intake of cadmium is dependent on the diet of an individual, food is generally the greatest source of cadmium exposure for non-smoking individuals. Food contamination by cadmium can occur from use of phosphate fertilizers, agricultural sewage applications, cadmium-plated utensils and equipment used in food preparation and processing, pottery glazes and plastic stabilizers. In a Total Diet Study performed by Gartrell, et al. (1986; ATSDR, 1997), adult intake of cadmium from food was estimated to be approximately 30 µg/day, with the largest contribution from grain, cereal products, and potatoes. Another study reported by Thornton, et al. (1992; ATSDR, 1997) indicates that the typical dietary intake of cadmium is 0.23 mg/week. The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1989; ATSDR, 1997) established a Proposed Tolerable Weekly Intake (PTWI) for cadmium of 7 µg/kg body weight for adults, infants and children (9.2 ug/day for a 9.2 kg child). JECFA noted that the typical dietary intake of cadmium is 1-4 ug/kg body weight/week (1.3-5.25 ug/day for 9.2 kg child), thereby suggesting that there is only a small safety margin between normal dietary exposure and exposure that is capable of producing adverse effects. A total diet study performed by the FDA (1993; EPA, 1999) suggests that the mean lifetime exposure to total cadmium from all food is 10 ug/person/day or 0.14 ug/kg/day for a 70-kg adult. The FDA considers the tolerable daily intake of cadmium to be 55 ug/person. They estimate that the dietary intake of cadmium (without consideration of shellfish) to be approximately 20% of the tolerable daily intake, 10 ug/person/day (FDA, 1993). Because the diet is the main source of background exposure to cadmium in the general population, the EPA has defined 0.14 ug/kg/day as the mean daily lifetime exposure to total cadmium.

In areas where cadmium-emitting industries are not present, the intake of cadmium from drinking water or ambient air is of minor significance (ATSDR, 1997). Cadmium levels in drinking water are usually negligible, with the average reported level being 0.5 ug/L (ATSDR,

1997). Most drinking water supplies in the United States do not contain more than 1 ug/L cadmium, but the concentration of cadmium has been recorded as high as 10 ug/L in areas impacted by industrial discharge or leachate from metal or plastic pipes (ATSDR, 1997). Near sources of cadmium pollution, individuals may inhale concentrations of cadmium that could contribute significantly to cadmium intake with the average inhaled dose being 1-75 ug Cd/day. Cadmium levels in urban air are reported to be in the range of 5 to 40 ng/m³, while in rural areas levels are typically in the range of 1 to 5 ng/m³ (ATSDR, 1997). The typical concentration of cadmium in soil is 260 ppb (ATSDR, 1997).

Subpopulations, such as smokers and shellfish eaters, have a much greater risk for cadmium-induced adverse effects. Because the background levels of cadmium are so high and only limited information is available concerning variability in these levels, the EPA has suggested that any assessment addressing cadmium exposure must consider the background contribution when deriving recommended risk levels. As smokers have been estimated to be exposed to 1.7 ug Cd/cigarette (ATSDR, 1997), the amount of cadmium to which smokers are exposed is roughly the same as that ingested in the diet. However, it has been shown that passive smoking does not appear to increase blood cadmium concentrations (ATSDR, 1997). Therefore, the presence of a smoker in a child's environment should not significantly increase the child's daily intake of cadmium.

With the assumption that the typical dietary exposure cited by JEFCA adequately accounts for the minimal exposure from drinking water and ambient air, the maximum daily intake for a 9.2 kg child can be estimated to be 5.25 ug/day ((4 ug/kg body weight/week * 9.2 kg) / 7 days). Similarly, as discussed above, the EPA/FDA estimates the daily exposure to total cadmium in an average 9.2 kg infant as 1.3 ug/day (0.14 ug/kg/day * 9.2 kg).

3.3 Determination of acceptable limits for finished products.

The derivation of an acceptable limit for finished products was based on the Joint FAO/WHO Expert Committee on Food Additives Provisional Maximum Tolerable weekly intake (PTWI) for cadmium of 0.007 mg/kg body weight. A calculated tolerable daily intake would be 0.001 mg/kg body weight. Assuming a 60 kg adult, this would result in a tolerable daily intake of 0.06 mg cadmium.

With a 10% allocation to dietary supplements an acceptable limit for finished products containing cadmium would be 0.006 mg/day

The JECFA PTWI was chosen, from the available data, to derive an acceptable limit because The World Health Organization had looked at a large compilation of data on exposure in Europe. JECFA looked at cadmium as a contaminant in food. They examined data on the dietary intake of cadmium in a wide variety of countries, worldwide based on the amount of cadmium found in foods. In addition, the chemical identity and bioavailability of cadmium in foods was investigated. Based on this information, it was determined that there is only a relatively small safety margin between exposure in the normal diet and exposure that produces deleterious effects.

3.4 Determination of acceptable limits for raw materials.

The acceptable limit for cadmium in raw materials was taken from the WHO Monographs on Selected medicinal plants and is 0.3 ppm.

4.0 CHROMIUM (VI)

4.1 REGULATORY STATUS

4.1.1 USEPA

The USEPA calculated a preliminary chronic oral reference dose (RfD) for chromium (VI), relevant to *soluble* salts of chromium, at 0.005 mg/kg/day (IRIS, 1998). This value is based on a NOAEL for systemic effects in rats exposed to 2.5 mg/kg/day Cr³⁺, as potassium chromate in the drinking water for 1 year in the study by MacKenzie et al. (1958). This NOAEL was divided by two 10-fold uncertainty factors to account for expected interspecies and intraspecies variability. Another 3-fold modifying factor is applied to address the human effects observed in a study of Zhang and Li (1987), in which high doses of chromium in drinking water were correlated with gastrointestinal effects such as diarrhea, stomach ache, indigestion, vomiting, and stomach cancer. The quantitative data in this study were not reported according to acceptable protocol (exposure data limited, duration of exposure unknown, confounding factors not discussed), and were therefore disregarded for further use in respect to derivation of the oral RfD. In response to peer review comments of the ATSDR document (February, 1999), an additional 3-fold modifying factor was also included to adjust the NOAEL to compensate for the less-than-lifetime exposure duration in the MacKenzie study. Therefore, the total uncertainty factor was set at 900, and the resulting RfD of 0.003 mg/kg/day was calculated (NOAEL / 900).

4.1.2 USFDA

The USFDA has selected a Reference Daily Intake for chromium of 120 ug/day based on adult exposures. There is very little data on child exposures, and none of that data is appropriate for use in determining recommended chromium exposures for children (USDHHS, 1995).

4.1.3 California Proposition 65

The No Significant Risk Level (NSRL) for chromium inhalation exposure in a 70 kg adult is 0.000001 mg/day (1×10^{-6} mg/day), or 0.000000014 mg/kg/day (1.4×10^{-8} mg/kg/day), with respect to risk of cancer.

The State of California, under Prop 65, has not established an Acceptable Intake Level (AIL) for chromium exposures, with respect to potentially adverse reproductive effects.

4.1.4 Other Regulatory Values

The Committee on Dietary Allowances, Food and Nutrition of the National Research Council has recommended an Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 50-200

ug/day for adults based on the absence of chromium-deficiency signs in the major part of the U.S. population consuming an average of 50 ug chromium/day (NRC, 1989). This is equivalent to 0.71-2.9 ug/kg-day for a 70 kg adult $[(50 \text{ ug/day}) / 70\text{kg} = 0.71 \text{ ug/kg-day}]$, and $(200 \text{ ug/day}) / 70 \text{ kg} = 2.9 \text{ ug/kg-day}$. The NRC has not proposed an ESADDI value for children, based on a lack of data.

ATSDR has adopted the upper range of the estimated safe and adequate daily dietary intake of 200 ug/day as an interim guidance for oral exposure to chromium (III) and chromium (VI), (February, 1999).

4.2 Estimation of Maximum Daily Intake

An adult in the general population of the United States has an estimated average daily intake of 60 ug of Cr/day, based on exposures from air, water, and food (Toxicological Profile for Chromium (Update), (ATSDR, 2000). Exposures for children may be assumed to be linearly related to those for adults, based upon no evidence to the contrary. Therefore, a 9.2 kg child would typically be exposed to an average daily intake of 8 ug/day $[(60 \text{ ug/day})/70\text{kg} \times 9.2 \text{ kg} = 8 \text{ ug/day}]$. Long-term supplementation trials in humans receiving 150 ug/day in addition to the dietary intake have established the safety of an intake of 200 ug/day. Regular dietary intakes of approximately 200 ug/day have been reported in several studies with no adverse effects known (NRC, 1989). Therefore, in order to avoid adverse effects, total exposure to chromium on a daily basis should not exceed 200 ug/day in an average adult in the general population, the upper bound of the ESADDI of 50-200 ug/day (ATSDR, 1999). Note that it has not been determined how much chromium above 200 ug/day may be detrimental, but this is the highest value that has been examined, and it was without observed adverse health effects. On the low end of this range, chromium deficiency was absent in a majority of the US population consuming an average of 50 ug/day or more (NRC, 1989). For children, the linear equivalent of this upper bound value is 30 ug/day $[(200 \text{ ug/day})/70 \text{ kg} \times 9.2 \text{ kg} = 30 \text{ ug/day}]$.

4.3 Determination of acceptable limits for finished products.

The derivation of an acceptable limit for finished products was based on the EPA RfD of 0.003 mg/kg body weight per day. The EPA RfD was chosen to derive the acceptable limit as the EPA risk assessment was considered to be the best and most comprehensive of the assessments available. The EPA RfD is supported by the ATSDR data. Assuming a 60 kg adult, this would result in an acceptable daily intake of 0.18 mg chromium.

With a 10% allocation to dietary supplements an acceptable limit for finished products containing chromium would be 0.02 mg/day (rounded).

4.4 Determination of acceptable limits for raw materials.

The derivation of an acceptable limit for the raw materials was also based on the EPA RfD for chromium of 0.003 mg/kg body weight per day. Assuming 60 kg adult, an extraction factor of 1, an average daily dose of dietary supplement of 1 gram and a safety factor of 100, this would result in an acceptable daily intake of 2 mg chromium.

5.0 LEAD

5.1 REGULATORY STATUS

This section includes a brief summary of the current and/or pending regulatory status of the metal, as well as some background on the development of the regulatory value.

5.1.1 USEPA

5.1.1.1 USEPA IRIS Substance File

The EPA has considered it inappropriate to derive an oral RfD for inorganic lead. This is due to the harmful effects occurring at blood lead levels for which a threshold cannot be established. These harmful effects include changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development. While there are inadequate human carcinogenicity data, lead has been classified as a Group B2 probable human carcinogen due to sufficient animal evidence. Ten rat bioassays and one mouse assay have shown statistically significant increases in tumor incidence. Information was not available for an RfC for chronic inhalation exposure as of September 1999.

5.1.1.2 USEPA MCLG

The EPA proposed to set the MCLG for lead at zero in August 1988 (53 FR 31516). The proposed MCLG was based on the three primary considerations. First, a variety of low-level health effects have been identified for which it is difficult to establish a clear threshold exposure level below which there is minimal risk of adverse health effects. The EPA cited studies that demonstrated adverse health effects at blood lead levels at or below 10 µg/dl, which is less than the current level of concern of 10-15 µg/dl (56 FR 26468). Second, the EPA has established a policy goal that drinking water should contribute minimal lead to the total lead exposure. The EPA has established a clear correlation between water lead and blood lead levels, thereby confirming that lowering the water lead level can reduce a significant portion of the total lead exposure (56 FR 26469). Lastly, lead has been classified as a Group B2 probable human carcinogen. With these considerations, the MCLG of zero for lead was finalized in June 1991 (56 FR 26467).

5.1.1.3 USEPA Action Level

The EPA has set an action level for lead of 0.015 mg/L in the 90th percentile of first-draw tap water samples from small and medium systems (fewer than 50,000 people). In selecting the action level, the Safe Drinking Water Act mandates that the EPA take into consideration technical feasibility (56 FR 26490). If a system fails to meet the lead action level, it is not in violation as long as corrosion control has been optimized. If corrosion control has not been optimized, failure of a system would initiate the installation or improvement of corrosion control and public education. The EPA concludes that 0.015 mg/L at the 90th percentile will provide substantial health protection for children (56 FR 26491).

5.1.2 USFDA

The FDA action levels are established based on the unavoidability of exposure to the substance and do not represent permissible levels of contamination (FDA 1994). Action levels represent limits at or above which the FDA will take legal action to remove products from the market.

The FDA has accepted lead exposures under the following conformances:

- 3.0 µg/mL lead in leaching solution for ceramic flatware (average of 6 units) (57 FR 29734-29736).
- 2.0 µg/mL lead in leaching solution for small hollowware (any 1 of 6 units) (57 FR 29734-29736).
- 1.0 µg/mL lead in leaching solution for large hollowware (any 1 of 6 units) (57 FR 29734-29736).
- 0.5 µg/mL lead in leaching solution for cups and mugs (any 1 of 6 units) (57 FR 29734-29736).
- 0.5 µg/mL lead in leaching solution for pitchers (any 1 of 6 units) (57 FR 29734-29736).
- 3 µg/mL lead in leaching solution for ceramic flatware (average of 6 units) (57 FR 29734-29736).
- 7.0 µg/mL lead for silver-plated hollowware - products intended to be used by adults (average of 6 units) (CPG 7117.05).
- 0.5 µg/mL lead for silver-plated hollowware - products intended to be used by infants and children (any 1 of 6 units) (CPG 7117.05).

FDA toxicologists have derived provisional total tolerable intake levels (PTTILs) of lead from all sources of exposure. For pregnant women, the PTTIL was set at 25 µg/day, while for infants, the PTTIL was set at 6 µg/day (FDA Consumer 8/93). PTTILs represent the intake levels that the FDA believes provide a reasonable margin of protection from the toxic effects of lead from all food and non-food sources.

5.1.3 World Health Organization

The Joint FAO/WHO Expert Panel on Food Additives established a provisional tolerable weekly intake (PTWI) value of 25 µg of lead per kg of body weight (JECFA 2000). JECFA first evaluated lead at its sixteenth meeting, when a provisional tolerable weekly intake (PTWI) of 3 mg of lead per person, equivalent to 50 µg/kg body weight, was established. This PTWI was reconfirmed by the Committee at its twenty-second meeting. At its thirtieth meeting the

Committee assessed the risk posed by lead to the health of infants and children and established a PTWI of 25 µg/kg body weight for this population group. The Committee again evaluated lead at its forty-first meeting, when the previous PTWI of 50 µg/kg body weight for adults was withdrawn, and the existing PTWI of 25 µg/kg body weight for infants and children was reconfirmed and extended to people in all age groups. The review of the health effects of lead at the forty-first meeting was based on an assessment of inorganic lead performed by an International Programme on Chemical Safety (IPCS) Task Group and published as an Environmental Health Criteria monograph (IPCS, 1995).

5.1.4 California Proposition 65

Proposition 65 is the common name for *California's Safe Drinking Water and Toxic Enforcement Act of 1986*. Among other requirements, Proposition 65 requires the Governor of California to publish a list of chemicals that are known to the State of California to cause cancer, birth defects, or other reproductive harm. California Proposition 65 has inorganic lead listed as a reproductive toxicant with an Acceptable Intake Level (AIL) of 0.5 µg/day. The value represents the no observable effect level (NOEL) for lead divided by an uncertainty factor of 1,000. A "No Significant Risk Level" or NSRL, calculated for Proposition 65 carcinogens, has not been determined for lead.

5.1.5 Other Regulatory Values

CDC

The CDC has set a blood lead level of concern at 10 µg/dL (CDC 1991). Several studies demonstrated neurobehavioral impairment in lead exposed children with blood lead levels as low as 10 to 14 µg/dL.

OSHA

The Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit (PEL) of lead in workroom air at 50 µg/m³ averaged over an 8-hour workday for workers in general industry.

5.2 Estimation of Maximum Daily Intake

Exposure of the general population to lead is most likely to occur through the ingestion of contaminated food and drinking water, and by the inhalation of lead particles in ambient air. Direct inhalation of lead accounts for only a small part of the total human exposure; however, lead that is adsorbed to soil may be inhaled as dust and reentrainment of lead-contaminated dust is common (ATSDR, 1999). The CDC has concluded that the most common source of lead exposure for children is lead-based paint that has deteriorated into paint chips and lead dusts, and the most common sources of lead exposure for adults are occupational (CDC, 1997). In 1990, the FDA estimated that toddlers (2-year olds) received 16% of their total lead exposure from food, 1% from soil, 7% from water, and 75% from dust (ATSDR, 1999). Baseline estimates of potential human exposure to dusts, including intake due to normal hand-to-mouth activity, are

0.2 g / day for children 1-6 years old versus 0.1 g / day for adults when both indoor and outdoor ingestion of soil including dust are considered (ASTDR, 1999).

In 1990, the EPA estimated that lead intake from U.S. drinking water was, on average 11 ug /day for a 6-year-old child and 7.5 ug/day for an infant less than 1 year old (ATSDR, 1999; Cohen 1988b). A study of lead in the diet of Canadian infants found that the average intake by children 0-1 years of age to be 16.5 ug/day when ingestion of both food and water was considered (ATSDR, 1999; Dabeka and McKenzie 1988).

Based on the data from the FDA's Total Diet Food Studies, baseline values for average daily intake of lead by consumption of food, water, and beverages are presented in Tables 1 and 1b.

Table 1. Daily average intake of lead (ug lead / day) by consumption of food, water and beverages (ATSDR, 1999).

AGE	SEX	1980	1986	1990
6-11 months	Male/female	34	10	3.8
2 years	Male	45	12.8	4.3
14 – 16 years	Female	No data	15.2	6.1
14 – 16 years	Male	No data	21.8	8.5
25-30 years	Female	No data	14.8	6.7
25 – 30 years	Male	84	21.2	8.5
60 –65 years	Female	No data	15.6	2.2
60 –65 years	Male	No data	19.1	8.1

Table 1b. Estimation of daily lead intake (ATSDR, 1999).

FDA Estimate of lead intake from Food, Water and Beverages (ATSDR, 1999;)	EPA Estimate of lead intake from U.S. Drinking Water (ATSDR, 1999; Cohen 1988b)	Average intake of lead in the diet of Canadian infants (ATSDR, 1999; Dabeka and McKenzie 1988).
3.8 ug/day (< 1 year old male and female)	7.5 ug/day (< 1 year old)	16.5 ug/day (< 1 year old male and female)
4.3 µg/day (2 year old- male)	11 µg/day (6 year old)	

More recent data have demonstrated declining lead exposures for all age groups as a result of reduced lead solder in cans and the phase-out of leaded gasoline.

5.3 Determination of acceptable limits for finished products.

The derivation of an acceptable limit for finished products was based on the JECFA PTWI of 0.025 mg/kg body weight. The JECFA number was selected for the acceptable limit derivation 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. A tolerable daily intake calculated from this would be 0.004 mg/kg body weight. Assuming a 60 kg adult, this would result in an acceptable daily intake of 0.24 mg inorganic arsenic.

With a 10% allocation to dietary supplements an acceptable limit for finished products containing lead would be 0.02 mg/day (rounded).

5.4 Determination of acceptable limits for raw materials.

The acceptable limit for lead in raw materials was taken from the WHO Monographs on Selected Medicinal Plants and is 10 ppm.

6.0 MERCURY

6.1 REGULATORY STATUS

Mercury can be organized under three different headings, metallic mercury (elemental mercury), inorganic mercury, and organic mercury. Elemental mercury is typically used in thermometers and electrical switches. Inorganic mercury occurs when mercury combines with elements such as sulfur, oxygen and chlorine. These compounds are generally referred to as salts of mercury. They are generally used as fungicides, topical antiseptics or disinfectant agents. Lastly, when

mercury combines with carbon you have the organic form of which the most common is methylmercury. All forms will exist naturally in the environment.

The toxicokinetics of mercury is highly dependent on the form of mercury to which a person is exposed. Elemental mercury is absorbed through the lungs quite rapidly but poorly from the gastrointestinal tract. Once absorbed, it is readily distributed throughout the body. Inorganic mercury absorption through the gastrointestinal tract varies with the particular mercuric salt involved. On the other hand methylmercury is rapidly and extensively absorbed through the gastrointestinal tract. Regardless of the form of mercury, the nervous system appears to be the most sensitive endpoint for elemental and methylmercury. Information on inorganic mercury suggests the most sensitive endpoint to be mercury induced autoimmune glomerulonephritis. Based on this information it is the opinion of the reviewer that limit values derived using a surrogate (e.g. methyl mercury vs. elemental mercury) may over estimate the potential health effects from exposure. One potential source of exposure for the general population is through dental amalgams. Estimates of exposure from this source range from 3 to 17 micrograms per day (ug/day). Another primary source of organic mercury exposure is ingestion of fish, shellfish or marine mammals. The FDA has estimated that on average, most people are exposed to 50 nanograms per kilogram body weight per day (50 ng/kg/day). This equates to a daily exposure for a 70 kg adult male of 3.5 micrograms (ug). A currently FDA action level for fish products is 1.0 mg/kg. Several cases of poisonings via contaminated grains are also cited as a basis of regulations. As noted previously mercury exposure can occur from methyl, inorganic or elemental mercury. Once it enters the body the form most readily absorbed is methylmercury, > 95%, followed by inorganic mercury, 10-40%, and elemental mercury, < 0.1 % (ASTDR, 1999).

Systemic toxicity from inhalation exposure to metallic mercury vapor ranges from lung, stomach and intestinal damage. Increased heart rates, abnormal heart rhythms, elevated blood pressure, and kidney damage are observed with inorganic mercury exposure. As well, teratogenic effects can occur during critical periods of the fetus development. However the most sensitive health endpoint for exposure to mercury is the neurological effects associated with the developing fetus.

6.1.1 USEPA

Available toxicological and epidemiological data was evaluated using U.S. EPA risk assessment guidelines and methodologies. The data supported a quantitative assessment of systemic toxicity but were not sufficient to generate a quantitative risk assessment for carcinogenicity or developmental toxicity. For elemental mercury, an inhalation RfC was calculated. For inorganic and methylmercury oral reference doses (RfD) were calculated.

Elemental mercury

An inhalation RfC of 3.0×10^{-4} mg/m³ was established by the U.S. EPA Mercury RfC workgroup based on the following critical effects observed in humans, hand tremors, increase in memory disturbance and slight subjective and objective evidence of autoimmune dysfunction in adults (Fawer, et al., 1983). No oral RfD was established based on the oral toxicokinetics of elemental mercury.

Inorganic mercury

An oral RfD of 3.0×10^{-4} mg/kg was established for mercuric chloride by the U.S. EPA Mercury RfD workgroup based on the critical effects of mercury-induced autoimmune glomerulonephritis (U.S. EPA, 1987)

Methylmercury

An oral RfD of 1.0×10^{-4} mg/kg has been established for methylmercury by the U.S. EPA based on a principle human study in rural Iraq (Marsh et.al.1987) and supported by an FDA risk assessment of the Tollefson and Cordle, 1986 study.

6.1.2 USFDA

The U.S. FDA has established an action level of 1.0 mg/kg (FDA, 1979) for food and animal feed (fish, shell fish, crustaceans, other aquatic mammals, fresh, frozen or processed) that is based on consumption of 7 ounces of fish weekly. Faults noted in this risk assessment consisted of a statement that the limit of 1.0 mg/kg mercury in marine fish and mammals provides a sufficient margin of safety for young children and for those consumers exceeding the acceptable daily intake. In 1984 the FDA converted from a mercury standard to one based on methylmercury. This action level takes into consideration the tolerable daily intake for methylmercury, as well as information on seafood consumption and other sources of exposures to methylmercury. Based on information available in the Iraqi study in 1974, the FDA has acknowledged that the fetus may be more sensitive than adults to the effects of mercury. However due to uncertainties associated with this study the agency has chosen not to revise its action level. They are currently waiting for findings from the Seychelles Island and Faroes Islands studies.

The Seychelles study was conducted on a cohort of mother – child pairs in the Republic of Seychelles, a western archipelago in the middle of the Indian Ocean where 85 % of the population consumes marine fish daily. The outcome measures were prenatal and postnatal exposure and six age appropriate neurodevelopment tests. The objective of the study was to study the association between methylmercury exposure and the developmental outcomes of children at 66 months of age.

The Faroe Islands study was conducted on a cohort of 1022 singleton births during a 21 month period between 1986 – 1987. The hypothesis was that in this small nordic community that had a wide range of seafood intake and limited social differences, excessive mercury exposure would be related to decreased neurobehavioral function. AT approximately 7 years of age, testing was conducted on 917 of the remaining cohort members.

6.1.3 World Health Organization

The Joint FAO/WHO Expert Committee on Food additives first evaluated methylmercury at its sixteenth meeting, when it established a provisional tolerable weekly intake (PTWI) of 300 µg of total mercury per person, of which no more than 200 µg should be present as methylmercury. At its twenty-second and thirty-third meetings, the PTWI of 200 µg of methylmercury (3.3 µg/kg body weight) for the general population was confirmed (JECFA 2000).

6.1.4 California Proposition 65

On May 1, 1996, Methylmercury compounds were added to the State of California EPA list of Chemicals Known to the State to Cause Cancer for exposures of 1×10^{-5} mg/kg/day. There has not been a No Significant Risk Level (NSRL) established for methylmercury exposures under Proposition 65.

In addition, both methylmercury, elemental mercury and mercury compounds are listed on the Chemicals Known to the State to Cause Reproductive Toxicity, specifically developmental toxicity. The State of California, under Prop 65, has established an Acceptable Intake Level (AIL) for methylmercury as a Reproductive Toxicant at 0.3 ug/day for a 70 kg adult.

6.2 Estimation of Maximum Daily Intake

Inhalation, and ingestion are the primary routes of human exposure to methylmercury and methylmercury compounds (ATSDR, 1999). While dietary intake of methylmercury is dependent on the diet of an individual, contaminated seafood is in many populations the primary and greatest source of methylmercury exposure. Oral exposure to methylmercury generally occurs through food, fish, shellfish, marine mammals, plants, consumer and medicinal products, cigarettes and through religious rituals ceremonies and practices. According to Fishbein, 1991, the mean range of mercury concentrations in food stuffs is 0.4 ug/g to 0.004 ug/g. The World Health Organization (WHO) has estimated the average daily intake of mercury and mercury compounds to be, 3 to 17 ug/day (elemental mercury vapor), Inorganic mercury compounds (0.3 ug/day), and Methylmercury (2.31 ug/day). Dental amalgams are also a major contributing factor in body burden (ATSDR 1999).

In 1984 the FDA conducted a total dietary study to estimate the average daily intake of total mercury (Gunderson 1988). Estimated daily exposures for mercury were 0.49 ug/day (infants 6-11 months), 1.3 ug/day (2 yr. old), 2.9 ug/day (females 25-30 yr. old), 3.9 ug/day (males 25-30 yr. old). Expressed as a per body weight basis, 2 yr. olds are 0.1 ug/kg/day and all other age groups, 0.05 mg/kg/day. In a second study, (ATSDR 1999), dietary information on 120, 000 adults was compiled. The estimated average daily intake for females was 8.2 ug/day (0.123 ug/kg/day), and males 8.6 ug/day (0.126 ug/kg/day). The author noted that the coefficient of variation for mercury was 44.0 %, indicating that the estimates may be accurate to within a factor of two.

The WHO Environmental Health Criteria (ATSDR, 1999) established a Proposed Tolerable Weekly Intake (PTWI) for methylmercury of 3.3 $\mu\text{g}/\text{kg}$ body weight, and 5.0 $\mu\text{g}/\text{kg}$ body weight total. Other guidelines and or regulations are as noted: WHO drinking water guideline for health-related organic (0.001 mg/L), EPA Office of Drinking Water Maximum Contaminant Level, 0.002 mg/L, FDA, Action level for deleterious substances in human food and animal feed, 1 ppm, Bottled Water 0.002 ug/L.

In areas where methylmercury-emitting industries are not present, the intake of methylmercury from drinking water or ambient air is of minor significance (ATSDR, 1999). Methylmercury levels in drinking water are usually negligible, with the average reported level being

< 0.025 ug/L (US EPA Code of Federal Regulations. 40 CFR 125., 1984; ATSDR, 1999). Most drinking water supplies in the United States do not contain more than 0.5 ug/L methylmercury, but the concentration of methylmercury has been recorded as high as 300 ug/L. at contaminated sites. Methylmercury levels in urban air are reported to be in the range of 10 to 20 ng/m³, with higher concentrations in industrial areas (EPA, 1980; ATSDR, 1999). The typical concentration of methylmercury in soil is 0.02 to 0.625 ppm (ATSDR, 1999).

With the assumption that the typical dietary exposure cited by WHO adequately accounts for the minimal exposure from food, drinking water and ambient air, the maximum daily intake for a 9.2 kg child can be estimated to be 6.57 ug/day total mercury ((5 ug/kg body weight/week * 9.2 kg) / 7 days). and 4.3 ug/day methylmercury ((3.3 ug/kg body weight/week * 9.2 kg) / 7 days). Similarly, as discussed above, the EPA/FDA estimates the daily exposure to total methylmercury in an average 9.2 kg infant as 1.3 ug/day (0.14 ug/kg/day * 9.2 kg).

6.3 Determination of acceptable limits for finished products.

The derivation of an acceptable limit for finished products was based on the EPA RfD for inorganic mercury of 0.0003 mg/kg body weight per day. The EPA RfD was chosen to derive the acceptable limit as the EPA risk assessment was considered to be the best and most comprehensive of the assessments available. Assuming a 60 kg adult, this would result in an acceptable daily intake of 0.02 mg inorganic mercury.

With a 10% allocation to dietary supplements an acceptable limit for finished products containing lead would be 0.002 mg/day (rounded).

6.4 Determination of acceptable limits for raw materials.

The derivation of an acceptable limit for the raw materials was also based on the EPA RfD for inorganic mercury of 0.0003 mg/kg body weight per day. Assuming 60 kg adult, an extraction factor of 1, an average daily dose of dietary supplement of 1 gram and a safety factor of 100, this would result in an acceptable daily intake of 0.2 mg inorganic mercury.

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