

Elemental Impurities—Information

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ABSTRACT This *Stimuli* article presents the toxicological and regulatory bases for the elemental impurities limits specified in a proposed new *USP–NF* General Chapter. The article focuses on four metallic elements of known toxicity: arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg). The *Stimuli* article presents literature studies, along with the specific rationale for the proposed limits. This article also references the EMEA guidance on metal catalysts as a basis for certain other elemental impurities and presents specific considerations regarding dietary supplement products.

INTRODUCTION

The objective of this *Stimuli* article is to provide rationale in support of safe limits for certain elemental impurities in pharmaceuticals and dietary supplements. For pharmacopeial purposes, elemental impurities are defined as elements that are found in the environment or that are used or introduced in the manufacture of drug substances or excipients. The term *elemental impurities* is adopted here as an alternative to the ill-defined term *heavy metals*, and the highlighted elemental impurities include various transition metals and metalloids. In addition to catalysts or reagents normally used in chemical synthesis, sources of elemental impurities in pharmaceuticals could include minerals used in the manufacture of excipients, container–closure systems, and other product contact surfaces. Elemental impurities are those elements that are not completely removed by practical manufacturing techniques and should be evaluated relative to safety-based limits.

The permissible daily exposure (PDE) values provided for each highlighted elemental impurity have been adopted from published evaluations by regulatory bodies. USP has considered the rationale for reference doses (RfDs) published by the US Environmental Protection Agency (EPA) (1) as well as PDEs listed in the *Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents* (2). The EMEA guidance acknowledges that “owing to wide variability of the nature, quality, and quantity of toxicological data amongst the metal elements of interest, it is not possible to employ a totally consistent approach.” That is also the case for the PDE rationale highlighted below. To that end, USP will advise EMEA of inconsistencies, if any are found, in the data.

METHODS FOR ESTABLISHING EXPOSURE LIMITS

The PDEs ($\mu\text{g}/\text{day}$) were derived from the most sensitive toxicological endpoint using a standard set of assumptions for the risk assessment:

- 10 g/day dose for drug products for calculation of ppm limits
- 50-kg person for extrapolation from animal data on a body weight-basis
- 70-year lifetime
- 10% bioavailability for extrapolation from the oral PDE to the parenteral PDE.

Appropriate uncertainty factors were applied to the lowest no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL). The applied uncertainty factors span orders of magnitude and are considered adequate to account for the proportion of the total acceptable daily exposure attributable to drug product relative to other sources of exposure (i.e., food, water). Thus, adjustments for relative source contribution were not conducted.

CLASS 1 ELEMENTAL IMPURITIES

Arsenic (As)

Introduction

The natural abundance of arsenic in the Earth’s crust is about 1.8 ppm. Arsenic will partly substitute for phosphorus in biochemical reactions. The largest worldwide production of arsenic occurs in China. Arsenic is used in glass production, light-emitting diodes, and many other places.

Toxicokinetics: Absorption, Disposition, Metabolism, and Excretion (ADME)

Water-soluble inorganic arsenic compounds are absorbed through the GI tract (> 90%) and lungs; are distributed primarily to the liver, kidney, lung, spleen, aorta, and skin; and as much as 80% of a dose is excreted mainly in the urine within 61 hours following oral dosing (3–5). Pentavalent arsenic is reduced to the trivalent form and then is methylated in the liver to less toxic methylarsonic acids (4).

Toxicological Effects

Acute oral toxicity is characterized by GI and neurological effects (6), and acute oral LD₅₀ values range from about 10 to 300 mg/kg (4, 7). Low subchronic doses

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have resulted in immunosuppression, (8) and hepatorenal effects (9–14). Chronic exposures have resulted in mild hyperkeratosis and bile duct enlargement with hyperplasia, focal necrosis, and fibrosis (15, 16). Reduction in litter size, high male/female birth ratios, and fetotoxicity without significant fetal abnormalities have occurred following oral exposures (17–19). Parenteral dosing has resulted in exencephaly, encephaloceles, skeletal defects, and urogenital system abnormalities (20–23).

Human Toxicology

1. The data reported in these studies show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1,000 for the 20–39 year group, 10.5 per 1,000 for the 40–59 year group, and 20.3 per 1000 for the > 60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, a subsequent report indicates that the disease may not be due strictly to arsenic exposure (27). The data in Tseng et al. (25) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the study is considered a LOAEL.
2. The study by Cebrian et al. (28) shows an increase in skin lesions, 22% (64/296) at the high dose vs 2.2% (7/318) at the low dose in drinking water. The high dose was 410 µg/L and the low dose was 5–7 µg/L. For the dose estimates an average consumption of 3 L/day was used. No data are given regarding the arsenic exposure from food or the body weight of the participants. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng et al. (25) control group, but the dose is lower (0.4 vs 0.8 µg/kg/day).
3. The study by Southwick et al. (29) shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation) and arterial insufficiency in individuals exposed to arsenic. Exposure times are not clearly defined but are > 5 years, and dose groups are ranges of exposure. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian et al. (28) study. The incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh et al. (30) study described below. The dosed group may or may not be a LOAEL because the study does not report statistically significant effects in the dosed group compared to the control group.
4. This study (30) shows an increased incidence of abnormal clinical findings and abnormal electromyographic

findings with increasing dose of arsenic. However, the sample size is small. Percentages of abnormal clinical signs possibly attributed to As were 10%, 16%, and 40% at the low, middle, and high doses, respectively. Abnormal EMGs were 0%, 17%, and 53% in the same three groups. The average arsenic concentration of the low-dose wells was about 25 µg/L. The averages of the arsenic concentration in the middle- and high-dose wells were 70 and 680 µg/L, respectively.

5. Following is a summary of the defined doses in µg/kg/day from the principal and supporting studies:
 - (1) Tseng (24): NOAEL = 0.8; LOAEL = 14
 - (2) Cebrian et al. (28): NOAEL = 0.4; LOAEL = 22
 - (3) Southwick et al. (29): NOAEL = 0.9; LOAEL = none (equivocal effects at 6)
 - (4) Hindmarsh et al. (30): NOAEL = 0.7; LOAEL = 19 (equivocal effects at 2)

An uncertainty factor of 3 is used to account for the lack of data to preclude reproductive toxicity as a critical effect and to determine whether the NOAEL of the critical study accounts for all sensitive individuals.

Regulatory Assessment

Both IARC and EPA classify inorganic arsenic as carcinogenic to humans. The EPA RfD for chronic oral exposures, 0.3 µg/kg/day, is based on a NOAEL of 0.8 µg/kg/day and a LOAEL of 14 µg/kg/day for hyperpigmentation, keratosis, and possible vascular complications in a human population consuming arsenic-contaminated drinking water. To address uncertainties in the data, EPA states that “strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value.”

Conclusions

Based on the similarity of the findings, the oral RfD of arsenic is 0.3 µg/kg/day, and the recommended daily oral dose of 15 µg is based on a 50 kg person. Based on 10 g of drug product taken/day, a PDE of 1.5 µg/g (ppm) is derived. Under the assumption that the oral bioavailability is 10%, the parenteral PDE will be 1/10 of the oral PDE (i.e., 1.5 µg/day), resulting in an acceptable limit of 0.15 ppm.

Oral PDE: 0.3 µg/kg/day
Oral Daily Dose PDE: 15 µg/day
Oral Component Limit: 1.5 µg/g (ppm)
Parenteral Component Limit: 0.15 ppm.

Cadmium (Cd)

Introduction

Cadmium is a naturally occurring metal that is used in various chemical forms in metallurgical and other industrial processes and in the production of pigments. Environmental exposure can occur via the diet and drinking water (31). It has an abundance of approximately 0.15 ppm in the Earth's crust.

Toxicokinetics (ADME)

Cadmium is absorbed more efficiently by the lungs (30% to 60%) than by the GI tract, the latter being a saturable process (32). Cadmium is transported in the blood and is widely distributed in the body but accumulates primarily in the liver and kidneys (33). Cadmium burden (especially in the kidneys and liver) tends to increase in a linear fashion up to about 50 or 60 years of age, after which the body burden remains somewhat constant. Metabolic transformations of cadmium are limited to its binding to protein and nonprotein sulfhydryl groups and various macromolecules, such as metallothionein, which is especially important in the kidneys and liver (31). Cadmium is excreted primarily in the urine.

Toxicological Effects

Acute oral exposures of 20–30 g have caused fatalities in humans. Exposure to lower amounts may cause GI irritation, vomiting, abdominal pain, and diarrhea (31). An asymptomatic period of one-half to one hour may precede the onset of clinical signs. Oral LD₅₀ values in animals range from 63 to 1125 mg/kg, depending on the cadmium compound (34). Longer term exposure to cadmium primarily affects the kidneys, resulting in tubular proteinosis, although other conditions such as “itai-itai” disease may involve the skeletal system. Cadmium involvement in hypertension is not fully understood (33).

Regulatory Assessment

A concentration of 200 µg Cd/g wet human renal cortex is the highest renal level not associated with significant proteinuria (35). A toxicokinetic model can help to determine the level of chronic human oral exposure (NOAEL) that results in 200 µg Cd/g wet human renal cortex. The model assumes that 0.01% day of the Cd body burden is eliminated per day (35). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 5 and 10 µg/kg/day from water and food, respectively (i.e., levels that would result in 200 µg/g wet weight human renal cortex). Thus, based on an estimated NOAEL of 5 µg/kg/day for Cd in drinking water and an uncertainty factor (UF) of 10, an RfD of 0.5 µg/kg/day (water) was calculated. [NOTE: A UF of 10 is used to account for interhuman variability to the toxicity of this chemical in the absence of specific data about sensitive individuals.] An equivalent RfD for Cd in food is 1 µg/kg/day. Both values reflect incorporation of a UF of 10.

Using data from select environmental studies examining the relationship of urinary cadmium and the prevalence of elevated levels of biomarkers of renal function ATSDR issued the provisional Minimal Risk Level (MRL) for chronic cadmium exposure. The 95% lower confidence limit of urinary cadmium dose corresponding to the probability to exceed in 10% the risk of low molecular weight proteinuria has been estimated as 0.5 µg/g creatinine, assuming accumulation over a 55-year period. This value corresponds to an intake of 0.33 µg/kg/

day in females, for which, applying a safety factor of 3 for human variability ATSDR has set the MRL to 0.1 µg/kg/day.

Conclusions

Using the ATSDR MRL as the Oral PDE:

Oral PDE: 0.1 µg/kg/day.

Oral Daily Dose PDE: 5 µg oral per day.

Oral Component Limit: 0.5 µg/g (ppm)

Parenteral Component Limit: 0.05 ppm.

Lead (Pb)**Introduction**

Lead occurs naturally as a sulfide in galena. It is a soft, bluish-white, silvery gray, malleable metal with a melting point of 327.5°. Elemental lead reacts with hot boiling acids and is attacked by pure water. The solubility of lead salts in water varies from insoluble to soluble depending on the type of salt (36–38). Lead is a natural element that is persistent in water and soil. Most of the lead in the environment is from anthropogenic sources. The mean concentration is 3.9 µg/L in surface water and 0.005 µg/L in sea water. River sediments contain about 20,000 µg/g, and coastal sediments contain about 100,000 µg/g. Soil content varies with the location, ranging up to 30 µg/g in rural areas, 3,000 µg/g in urban areas, and 20,000 µg/g near point sources. Human exposure occurs primarily via diet, air, drinking water, and ingestion of dirt and paint chips (39–41).

Toxicokinetics (ADME)

The efficiency of lead absorption depends on the route of exposure, age, and nutritional status. Adult humans absorb about 10%–15% of ingested lead, but children may absorb up to 50%, depending on whether lead is in the diet, dirt, or paint chips. More than 90% of lead particles deposited in the respiratory tract are absorbed into systemic circulation. Inorganic lead is not efficiently absorbed through the skin, and consequently this route does not contribute considerably to the total body lead burden (42). Lead absorbed into the body is distributed to three major compartments: blood, soft tissue, and bone. The largest compartment is the bone, which contains about 95% of the total body lead burden in adults and about 73% in children. The half-life of bone lead is more than 20 years. The concentration of blood lead changes rapidly with exposure and has a half-life of only 25–28 days. Blood lead is in equilibrium with lead in bone and soft tissue. The soft tissues that take up lead are liver, kidneys, brain, and muscle. Lead is not metabolized in the body, but it may be conjugated with glutathione and excreted primarily in the urine (40, 42, 43). Exposure to lead is evidenced by elevated blood lead levels.

Toxicological Effects

The systemic toxic effects of lead in humans have been well documented by EPA (42–48) and ATSDR (40), who extensively reviewed and evaluated data reported in the literature up to 1991. The evidence shows that lead is a multitargeted toxicant, causing effects in the GI tract, he-

matopoietic system, cardiovascular system, central and peripheral nervous systems, kidneys, immune system, and reproductive system. Overt symptoms of subencephalopathic central nervous system (CNS) effects and peripheral nerve damage occur at blood lead levels of 40–60 $\mu\text{g}/\text{dL}$, and nonovert symptoms, such as peripheral nerve dysfunction, occur at levels of 30–50 $\mu\text{g}/\text{dL}$ in adults. No clear threshold is evident. Cognitive and neuropsychological deficits are not usually the focus of studies in adults, but there is some evidence of neuropsychological impairment (49) and cognitive deficits in lead workers with blood levels of 41–80 $\mu\text{g}/\text{dL}$ (50). Although similar effects occur in adults and children, children are more sensitive to lead exposure than are adults. Irreversible brain damage occurs at blood lead levels $\geq 100 \mu\text{g}/\text{dL}$ in adults and at 80–100 $\mu\text{g}/\text{dL}$ in children. Death can occur at the same blood levels in children. Children who survive these high levels of exposure suffer permanent severe mental retardation.

Toxicology Studies

As discussed previously, neuropsychological impairment and cognitive (IQ) deficits are sensitive indicators of lead exposure. Both neuropsychological impairment and IQ deficits have been the subject of cross-sectional and longitudinal studies in children. One of the early studies reported IQ score deficits of four points at blood lead levels of 30–50 $\mu\text{g}/\text{dL}$ and one to two points at levels of 15–30 $\mu\text{g}/\text{dL}$ (51).

Detailed longitudinal studies have been conducted on children (starting at the time of birth) living in Port Pirie, Australia (52–57), Cincinnati, Ohio (58–61), and Boston, Massachusetts (62–67). Various measures of cognitive performance have been assessed in these children. Studies of the Port Pirie children up to 7 years of age revealed IQ deficits in 2-year-old children of 1.6 points for each 10- $\mu\text{g}/\text{dL}$ increase in blood lead, deficits of 7.2 points in 4-year-old children, and deficits of 4.4 to 5.3 points in 7-year-old children as blood lead increased from 10 to 30 $\mu\text{g}/\text{dL}$. No significant neurobehavioral deficits were noted for children, 5 years or younger, who lived in the Cincinnati, Ohio, area. In 6.5-year-old children, performance IQ was reduced by seven points in children whose lifetime blood level exceeded 20 $\mu\text{g}/\text{dL}$. Because of the large database on subclinical neurotoxic effects of lead in children, only a few of the studies have been included. EPA (42,48) concluded that there is no clear threshold for neurotoxic effects of lead in children.

In adults, the cardiovascular system is a very sensitive target for lead. Hypertension (elevated blood pressure) is linked to lead exposure in occupationally exposed subjects and in the general population. Three large population-based studies have been conducted to study the relationship between blood lead levels and high blood pressure. The British Regional Heart Study (BRHS) (68), the NHANES II study (48, 69–72), and Welsh Heart Programme (73, 74) comprise the major studies for the general population. The BRHS study showed that systolic pressure greater than 160 mm Hg and diastolic pressure greater than 100 mm Hg were associated with blood lead levels greater than 37 $\mu\text{g}/\text{dL}$ (68). An analysis of 9933 subjects in the NHANES study showed positive cor-

relations between blood pressure and blood lead among 12–74-year-old males but not females (69, 71), 40–59-year-old white males with blood levels ranging from 7 to 34 $\mu\text{g}/\text{dL}$ (70), and males and females greater than 20 years old (75). In addition, left ventricular hypertrophy was also positively associated with blood lead (75). The Welsh study did not show an association among men and women with blood lead of 12.4 and 9.6 $\mu\text{g}/\text{dL}$, respectively (73, 74). Other smaller studies showed both positive and negative results. EPA (48) concluded that increased blood pressure is positively correlated with blood lead levels in middle-aged men, possibly at concentrations as low as 7 $\mu\text{g}/\text{dL}$. In addition, EPA estimated that systolic pressure is increased by 1.5–3.0 mm Hg in males and 1.0–2.0 mm Hg in females for every doubling of blood lead concentration.

Regulatory Assessment

EPA has not developed an RfD for lead because it appears that lead is a nonthreshold toxicant, and it is not appropriate to develop RfDs for these types of toxicants. However, a maximum contaminant action level for lead of 15 $\mu\text{g}/\text{day}$ was recommended for drinking water (40 CFR 141.80). In 2004, FDA set the maximum allowable level for lead in bottled water at 5 $\mu\text{g}/\text{L}$. Assuming an average water consumption of 2 L/day, the recommended RfD is 10 $\mu\text{g}/\text{day}$.

Conclusions

Assuming that the lead in the drug product will be absorbed in a manner similar to that from water, the RfD developed by FDA is used as the Oral Daily Dose PDE:

- Oral PDE: 0.2 $\mu\text{g}/\text{kg}/\text{day}$
- Oral Daily Dose PDE: 10 $\mu\text{g}/\text{day}$
- Oral Component Limit: 1 $\mu\text{g}/\text{g}$ (ppm)
- Parenteral Component Limit: 0.1 ppm.

Mercury (Hg)

Introduction

Mercury is a naturally occurring element that exists in multiple forms and in various oxidation states. It is used in a wide variety of products and processes. In the environment, mercury may undergo transformations among its various forms and among its oxidation states. Exposure to mercury may occur in both occupational and environmental settings, the latter primarily involving dietary exposure (76).

Toxicokinetics (ADME)

Mercury's ADME depend on its form and oxidation state (76, 77). Organic mercurials are more readily absorbed than are inorganic forms. An oxidation–reduction cycle is involved in the metabolism of mercury and mercury compounds by both animals and humans (76). The urine and feces are the primary excretory routes. The elimination half-life is 35 to 90 days for elemental mercury and mercury vapor and about 40 days for inorganic salts (77).

Toxicological Effects

Ingestion of inorganic mercury salts may cause severe GI irritation, renal failure, and death with acute lethal doses in humans ranging from 1 to 4 g (76). Mercuric (divalent) salts are usually more toxic than are mercurous (monovalent) salts (77). Mercury is also known to induce hypersensitivity reactions such as contact dermatitis and acrodynia (pink disease) (78). Inhalation of mercury vapor may cause irritation of the respiratory tract, renal disorders, central nervous system effects characterized by neurobehavioral changes, peripheral nervous system toxicity, renal toxicity (immunologic glomerular disease), and death (76).

Toxicology Studies

Toxicity resulting from subchronic and chronic exposure to mercury and mercury compounds usually involves the kidneys and/or nervous system. The specific target and effect depend on the form of mercury (76). Organic mercury, especially methyl mercury, rapidly enters the central nervous system and results in behavioral and neuromotor disorders (76, 77). The developing central nervous system is especially sensitive to this effect, as documented by the epidemiologic studies in Japan and Iraq where ingestion of methyl mercury-contaminated food resulted in severe toxicity and death in adults and severe central nervous system effects in infants (79–82). Blood mercury levels of < 10 µg/dL and 300 µg/dL corresponded to mild effects and death, respectively (79). Teratogenic effects due to organic or inorganic mercury exposure do not appear to be well documented for humans or animals, although some evidence exists for mercury-induced menstrual cycle disturbances and spontaneous abortions (76, 80, 83).

A subchronic and chronic oral RfD of 0.1 µg/kg/day for methyl mercury is based on a benchmark dose of 1.1 µg/kg/day relative to neurologic developmental abnormalities in human infants (1, 84). A subchronic and chronic oral RfD of 0.3 µg/kg/day for mercuric chloride is based on immunologic glomerulonephritis (1). A LOAEL of 0.63 mg Hg/kg/day for mercuric chloride was identified (85). NOAELs were not available for oral exposure to inorganic mercury or methyl mercury.

Regulatory Assessment

EPA's existing RfD of 0.1 µg/kg/day is based on a poisoning episode in Iraq. Results for two large epidemiological studies in the Faroe Islands and Seychelles Islands have become available since the 1995 IRIS entry. The Faroe Islands study identified associations between in utero methyl mercury exposure and deficits on a number of endpoints, as did the New Zealand study. In contrast, the Seychelles Islands study found little or no evidence of impairment. These studies underwent a comprehensive review by the National Research Council (NRC) of the National Academy of Sciences, along with a smaller study from New Zealand. NRC performed benchmark dose (BMD) analyses of a number of neuropsychological endpoints from each study. In the assessment described here, EPA used the NRC analyses as the basis for the derivation of an RfD for methyl mercury. Based on BMD levels (lower limit on the BMD) for a number

of endpoints from the Faroe Islands study, as well as an integrative analysis of all three studies, an RfD for 0.1 µg/kg/day was derived. This included a total uncertainty factor of 10 for interhuman toxicokinetic and toxicodynamic variables.

Conclusions

The presence of methyl mercury in drug products is unlikely. Therefore, the EPA-recommended RfD for mercuric chloride is used as the Oral PDE.

Oral PDE: 0.3 µg/day

Oral Daily Dose PDE: 15 µg/day

Oral Component Limit: 1.5 µg/g (ppm)

Parenteral Component Limit: 0.15 ppm.

CLASS 2 ELEMENTAL IMPURITIES

The limits for Class 2 elemental impurities are those of the EMEA *Guideline on the Specification Limits for Residual Metal Catalysts for Metal Reagents* (2).

Dietary Supplement-Specific Issues

Dietary supplements are composed of dietary ingredients (herbs or other botanicals, minerals, amino acids, vitamins, and other substances used by humans to supplement the diet) plus other inert components used in their composition. The dietary ingredients from natural sources are subject to contamination with elemental impurities from water, air pollution, or soil and other agricultural inputs. Processing procedures, such as extraction of plant parts and purification, can result in concentration or dilution of the elemental contaminants. Dietary substances of synthetic origin may also be contaminated with elemental impurities that are derived from their manufacturing processes (catalysts and residual reagents). Dietary ingredients of marine origin (such as fish oil or algal products) can accumulate methyl mercury chloride and cadmium, representing special cases. Limits for such exceptional dietary ingredients should be addressed in their specific monographs. Speciation of arsenic and mercury is another issue of relevance for dietary supplements.

Dietary supplements are regulated as a subset of foods and limits for contaminants set for food items are applicable. Major sources of exposure were considered at the time of setting limits for dietary supplements, and these sources include the environment, drinking water, and food. Recent surveys of dietary supplement intakes (86) were also taken in consideration to apply a safety factor related to the number of dietary supplements taken by a sizable portion of the population. Proposed limits for dietary supplements were derived from the Provisional Tolerable Weekly Intake (PTWI), which is recommended by FAO/WHO. Average daily exposures (µg/day) of each elemental contaminant from air, food, and drinking water were subtracted from the PTWI. From the remaining daily intake allowance, a range safety factor was used to account for multiple dietary supplement intakes was used to calculate the PDE for dietary supplements. With this approach, the recommended limits are consistent with the limits proposed in *Chapter* (232) for drugs and

with the limits set by other organizations. (WHO herbal drugs, EP herbal drugs, Health Canada for Natural Health Products, and the American Herbal Products Association-AHPA).

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APPENDIX

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