USP <2232> Elemental Contaminants In Dietary Supplements

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Dietary Supplements: Background

- Dietary Supplements are composed of dietary ingredients + other components (excipients)
  - Herbs and other botanicals, Vitamins, Minerals, Amino Acids, Probiotics, Proteins
  - Wide range of dosage forms: tablets, capsules, soft-gels, chewable gels, powders
- Ingredients from natural sources are subject to contamination from water, air pollution, soil, agricultural inputs and processing procedures
  - A survey of 109 herbal products
    - 4 of 109 had elevated lead
    - 20 out of 109 had elevated cadmium
  - Some Ayurvedic medicines mix metal ash with herbs – contamination with extremely high levels of lead identified[2]

[1]Current Findings on the Heavy Metal Content in Herbal Drugs, U. Gasser, B. Klier, A.V. Kühn, B. Steinhoff, © Pharmeuropa Scientific Notes 2009-1

[2]A cluster of lead poisoning among consumers of Ayurvedic medicine, Laura Breeher, Marek A. Mikulski, Thomas Czeczok, Kathy Leinenkugel & Laurence J. Fuortes, International Journal of Occupational and Environmental Health Vol. 21 , Iss. 4,2015

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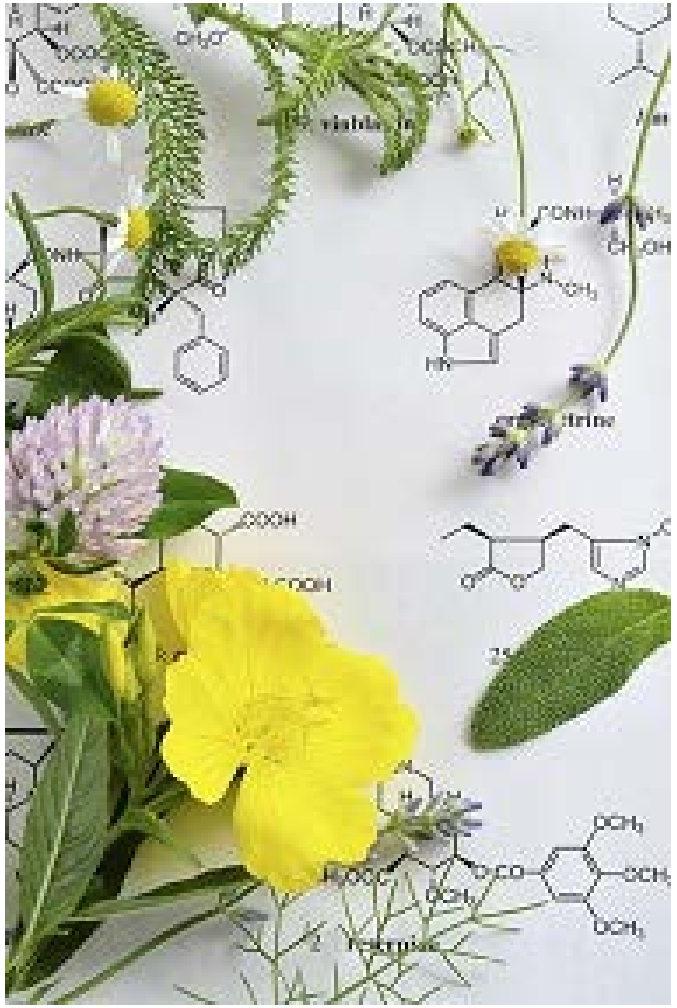
Dietary Supplements and the Need for Limits



Ginkgo biloba supplements found to be heavily contaminated with lead

https://ods.od.nih.gov/factsheets/list-all/BotanicalDietarySupplements/

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Dietary Supplement Regulation

- FDA regulates both finished dietary supplement products and dietary ingredients under a different set of regulations than those covering "conventional" foods and drug products.
- Dietary Supplement Health and Education Act of 1994 (DSHEA):
  - Manufacturers and distributors of dietary supplements and dietary ingredients:
    - Are prohibited from marketing products that are adulterated or misbranded.
    - Firms responsible for evaluating safety and labeling of products before marketing to ensure compliance with all DSHEA requirements and FDA regulations.
  - FDA is responsible for taking action against any adulterated or misbranded dietary supplement product after it reaches the market
- Unlike drugs, compliance with USP standards is voluntary in the US
- Compliance is enforceable only for supplements claiming to meet USP/NF standards through the misbranding provisions of the Act

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Chapter Objective

Limit amounts of elemental contaminants in finished dietary supplement dosage forms labeled as conforming to USP or NF standards

- Only covers finished dosage forms, not dietary ingredients
- Focused on the 4 major elements of toxicological concern
  - Arsenic (inorganic)
  - Cadmium
  - Lead
  - Mercury (total and methylmercury)
- Extent of testing - determined by risk-based approach that takes into account likelihood of contamination from source through manufacturing

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Permitted Daily Exposure

- Limits of elemental contaminants based on Permitted Daily Exposure (PDE)
- PDE derived from the Provisional Tolerable Weekly Intake (PTWI) recommended by Food and Agricultural Organization of the United Nations and World Health Organization (FAO/WHO)
  - Daily exposure (µg/day) derived for each elemental contaminant from air, food and water
  - PDE calculated by subtracting daily exposure from other sources
    - Based on average 50 kg body weight
    - Additional safety factor
- Other regulations (such as California Proposition 65) may require different limits
- Manufacturers are responsible for compliance with applicable local requirements differing from PDE values

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Limits of Elemental Contaminants

Element	PDE (µg/day)
Arsenic (Inorganic)	15
Cadmium	5
Lead	5
Mercury (total)	15
Methylmercury (as Hg)	2

- Arsenic – may be measured using nonspeciation procedure under assumption that all arsenic is inorganic – where limit is exceeded using nonspeciation procedure, compliance with the inorganic limit may be demonstrated using a speciation procedure
- Methylmercury determination is not required when content for total mercury is less than the limit for methylmercury

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Options for Compliance

- Dietary Supplement Analysis Option
- Individual Component Option
- Summation Option
- [Speciation procedures for inorganic arsenic and methyl mercury are provided in this chapter]

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Dietary Supplement Analysis Option

- This option is generally applicable
- The finished dietary supplement dosage form is analyzed based on the methods in Elemental Impurities – Procedures <233>
- Speciation procedures in <2232> should be used if necessary
- Analysis:
  - Calculate the measured amount of each elemental contaminant in µg/daily intake as:
    - Result = MVSS x N
    - Where
      - MVSS= measurement amount of each elemental contaminant (µg/serving size)
      - N = Maximum daily intake recommended in labeling (servings/day)

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Individual Component Option

- Applicable to finished dietary supplement dosage forms with maximum daily intake of NMT 10g of dietary supplement finished product
  - If all components in a formulation meet the limits given for the Individual Component Limits, these components can be used in any proportion without further calculation
- Unless otherwise specified in the monograph, proceed with analysis of individual components
  - Elemental Limits for use with the Individual Component Option

Element	Individual Component Limits (µg/g)
Arsenic (inorganic)*	1.5
Cadmium	0.5
Lead	0.5
Mercury (total)	1.5
Methylmercury (as Hg)*	0.2

*Speciation is not necessary when the total arsenic or mercury is less than the limit above

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Summation Option

- Option can be used
  - For any finished dietary supplement dosage forms that are consumed in quantities greater than 10 g/day
  - Where the acceptance limit for any contaminant in any component of the dietary supplement exceeds the applicable individual component limits
- Proceed with the analysis of the components (unless otherwise specified in the monograph)

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Summation Option: Calculation and Acceptance Criteria

- Calculate the amount of each elemental contaminant in µg/daily intake present in finished dietary supplement dosage form
  - Result = $\Sigma(C_i \times W_i) \times N$
    - C_i – elemental contaminant concentration in the individual component (µg/g)
    - W_i – weight of each individual component per serving of dietary supplement (g/serving)
    - N = maximum daily intake of supplement
  - Acceptance Criteria
    - The calculated amount of each elemental contaminant/daily intake is NMT the PDE

Element	PDE (µg/day)
Arsenic (Inorganic)	15
Cadmium	5
Lead	5
Mercury (total)	15
Methylmercury (as Hg)	2

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Questions

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Thank You

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