Pesticide Residues

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Botanical Monograph Approach

- USP limits for residues of 70 pesticides are set out in USP General Chapter <561> *Articles of Botanical Origin*, included in each botanical article's monograph by reference:

CONTAMINANTS

• MICROBIAL ENUMERATION TESTS ⟨2021⟩: The total bacterial count does not exceed 10 cfu/g, the total combined molds and yeasts count does not exceed 10 cfu/g, and the bile-tolerant Gram-negative bacterial count does not exceed 10 cfu/g.

• ABSENCE OF SPECIFIED MICROORGANISMS ⟨2022⟩: It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

• ARTICLES OF BOTANICAL ORIGIN, Pesticide Residues ⟨561⟩: Meets the requirements

<561> *Articles of Botanical Origin*

- For products marketed in U.S. as foods, including dietary supplements, <561> requires compliance to EPA (40 CFR 180) and FDA action levels (21 CFR 109; 21 CFR 509)
- Specifications in <561> are applicable to botanical drugs (e.g., psyllium husk), but not dietary supplements in U.S. (even for the same ingredient)

PESTICIDE RESIDUE ANALYSIS

Definition

Where used in this Pharmacopeia, the designation "pesticide" applies to any substance or mixture of substances intended to prevent, destroy, or control any pest, unwanted species of plants, fungus, or animals causing harm during or otherwise interfering with the production, processing, storage, transport, or marketing of pure articles. The designation includes substances intended for use as growth regulators, defoliants, or desiccants, and any substance applied to crops before or after harvest to protect the product from deterioration during storage and transport.

Limits

Within the United States, many botanicals are treated as dietary supplements and are subject to the statutory provisions that govern foods but not drugs in the Federal Food, Drug, and Cosmetic Act. Limits for pesticides in foods are determined by the Environmental Protection Agency (EPA) as indicated in the Code of Federal Regulations (40 CFR §180) or the Federal Register (FR). In addition, the FDA establishes action levels for unavoidable pesticide residues (21 CFR §109 and 21 CFR §509). For pesticide chemicals without EPA-established tolerance levels or FDA action levels, the residues should be below the detection limit of the specified method. Results less than the EPA detection limits are considered zero values. The limits contained herein, therefore, are not applicable in the United States when articles of botanical origin are labeled for food purposes. The limits, however, may be applicable in other countries. Unless otherwise indicated in the monograph, the article to be examined complies with the limits given in ▲*Table 5*▲ (USP 1-May-2019) The limits for suspected pesticides that are not listed in ▲*Table 5*▲ (USP 1-May-2019) must comply with the regulations of the EPA. For instances in which a pesticide is not listed in ▲*Table 5*▲ (USP 1-May-2019) or in EPA regulations, calculate the limit by the formula:

$$\text{Limit (mg/kg)} = AM/100B$$

where A is the acceptable daily intake (ADI), as published by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), in mg/kg of body weight; M is body weight, in kilograms (60 kg); and B is the daily dose of the article, in kilograms.

Limits for Botanical Extracts

- **EPA does not specify limits for botanical extracts which are ingested at lower levels than dried botanical raw materials**

USP <561>: If the article is intended for the preparation of extracts:

$$\text{Limit (mg/kg)} = AME/100B$$

A = ADI as published by FAO-WHO, in mg/kg of body weight
M = Body weight, in kg (60 kg)
E = *E*xtraction factor of pesticide in the preparation method, determined experimentally as the ratio between the original pesticide content in the plant material and the final pesticide content in the preparation
B = Daily dose of the extract, in kg

USP <565>: Botanical extracts might contain pesticide residues at either enriched or reduced levels compared to plant materials:

$$\text{If } E \leq 10\text{: Limit (mg/kg)} = L \times E$$

$$\text{If E > 10: Limit (mg/kg)} = AM/100B$$

L = Limit from chapter <561> or EPA tolerance or the FDA action level;
E = Plant to extract ratio
A = ADI as published by FAO-WHO, in mg/kg of body weight
M = Body weight, in kg (60 kg)
B = Daily dose of the extract, in kg

USP Limits for Pesticide Contaminants

- The MRLs in <561> are based on WHO-FAO ADIs, but are limited to the 90th percentile of the pesticide levels found on the herbs of commerce, i.e., readily accomplished under GACP
- USP compendial approach sets limits based on risk, and does not set not crop-specific limits
- USP <561> MRLs are harmonized with those of Ph. Eur.
- EPA MRLs are based on a submission from a pesticide manufacturer for intended uses of the pest control product on specific crops

Table ▲5▲ (USP 1-May-2019)

Substance	Limit (mg/kg)
Acephate	0.1
Alachlor	0.05
Aldrin and dieldrin (sum of)	0.05
Azinphos-ethyl	0.1
Azinphos-methyl	1
Bromide, inorganic (calculated as bromide ion)	125
Bromophos-ethyl	0.05
Bromophos-methyl	0.05
Bromopropylate	3
Chlordane (sum of *cis*-, *trans*-, and oxychlordane)	0.05
Chlorfenvinphos	0.5
Chlorpyriphos-ethyl	0.2
Chlorpyriphos-methyl	0.1
Chlorthal-dimethyl	0.01
Cyfluthrin (sum of)	0.1
λ-Cyhalothrin	1
Cypermethrin and isomers (sum of)	1

Pesticide Contamination in Botanical Ingredients

The Challenge:

- EPA established tolerances are plant/pesticide specific
- Unintentional pesticide contamination (point-source or non-point-source) due to environmental conditions is ubiquitous
- Zero-tolerance limit exists for any residue without specified level
- Zero tolerance is not useful for making safety based decisions – new technologies go to ppb levels

Most Botanicals Lack EPA Tolerances

LAB #	PRODUCT DESCRIPTION	TEST	RESULTS	LOT/LINE #
BO95445	Chamomile Flowers FC	Pesticides	**Carbendazim 0.03 ppm** Linuron <0.01 ppm	27219875/ Line 151-1
			Difenoconazole <0.01 ppm **Piperonyl butoxide 0.03 ppm**	
BO95446	Chamomile Flowers FC	Pesticides	**Carbendazim 0.02 ppm** Linuron <0.01 ppm	27219874/ Line 161-1
			Difenoconazole <0.01 ppm **Piperonyl butoxide 0.02 ppm**	

§180.127 Piperonyl butoxide; tolerances for residues.

(a) *General.* (1) Tolerances for residues of the insecticide piperonyl butoxide [(butyl carbityl)(6-propyl piperonyl)ether] are established in or on the following food commodities:

Commodity	Parts per million
Almond, postharvest	8
Apple, postharvest	8
Barley, postharvest	20
Bean, postharvest	8
Birdseed, mixtures, postharvest	20
Blackberry, postharvest	8
Blueberry, postharvest	8
Boysenberry, postharvest	8
Buckwheat, grain, postharvest	20

>2000 DS botanicals – they are not in EPA Crop Group 19 (aromatic and culinary herbs), nor is that practical since it is for pesticides intentionally applied.

What We Have Done So Far

- USP published a *Stimuli article* in *USP Pharmacopeial Forum 42(2)* in March 2016 regarding the issues surrounding limits for pesticide residues to ensure quality of articles of botanical origin, and to engage stakeholders to strengthen USP–NF contaminant standards

- Following up on the public comments in response to the *Stimuli article*, USP organized a **Roundtable Discussion** with stakeholders on December 7, 2016, to explore science-based solutions to address pesticide residues in botanical dietary ingredients and dietary supplements (for which, in the majority of cases, EPA has not established tolerances)

- We met with EPA and discussed specific examples, e.g., chamomile detained due to detection of piperonyl butoxide at 30 ppb while the fungicide is permitted by EPA at 8 ppm for blueberries, cherries and other fruits. USP <561> limit for piperonyl butoxide is 3 ppm (FAO ADI 0 – 0.2 mg/kg bw)

Next Steps

- **Further conversations with FDA, EPA, USDA, & NOP to discuss potential use of toxicologically-based pesticide residue limits in USP <561> as action levels for botanical dietary supplement ingredients:**
  - Discussion of <561> pesticide residue limits in minor crops, certified organic and certified wild-collected botanicals **as contaminants** under 21 CFR 111 could control the pesticide residues based on toxicology considerations
  - General MRLs could provide alternatives to the crop-specific limits: Canadian model - 0.1 ppm (but lower level for highly toxic pesticides with ADI < 0.002 mg/kg)

- **Update to chapter <561>: Need data!!!**
  - Expand the list of pesticides

Thank You

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BACKGROUND SLIDES - PESTICIDES

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Problem Statements

- Articles from an estimated 3,000 botanical species are in commerce yet majority of species have no EPA-established tolerances.
- Residues of “legacy” (e.g. DDT) and “current use pesticides” (CUPs) now detected in Arctic ice caps (long range atmospheric transport).
- Non-point source pesticide detection an increasing problem even with certified organically grown and/or wild-collected botanicals.
- In the absence of EPA-tolerances (= zero tolerance), residues of “allowed pesticides” intentionally applied to conventional herb crops in other countries are “unlawful pesticides” as per U.S. regulations.
- EPA does not specify limits for botanical extracts which are ingested at lower levels than dried botanical raw materials.
- Recent technological advancements in pesticide analysis have substantially improved the sensitivity of detection, identification, and quantitation of pesticide residues.
- USP limits are applicable to botanical drugs but not to botanical dietary supplements (even when same botanical can be a drug or supplement).

Pesticide limits in chapter <561>

Substance	Limit (mg/kg)
Acephate	0.1
Alachlor	0.05
Aldrin and dieldrin (sum of)	0.05
Azinphos-ethyl	0.1
Azinphos-methyl	1
Bromide, inorganic (calculated as bromide ion)	125
Bromophos-ethyl	0.05
Bromophos-methyl	0.05
Bromopropylate	3
Chlordane (sum of *cis*-, *trans*-, and oxychlordane)	0.05
Chlorfenvinphos	0.5
Chlorpyriphos-ethyl	0.2
Chlorpyriphos-methyl	0.1
Chlorthal-dimethyl	0.01
Cyfluthrin (sum of)	0.1
λ-Cyhalothrin	1
Cypermethrin and isomers (sum of)	1
DDT (sum of *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDT, *p,p′*-DDT, *o,p′*-TDE, and *p,p′*-TDE)	1
Deltamethrin	0.5
Diazinon	0.5
Dichlofluanid	0.1
Dichlorvos	1

Pesticide limits in chapter <561> (contd.)

Dicofol	0.5
Dimethoate and omethoate (sum of)	0.1
Dithiocarbamates (expressed as CS_2)	2
Endosulfan (sum of isomers and endosulfan sulphate)	3
Endrin	0.05
Ethion	2
Etrimphos	0.05
Fenchlorophos (sum of fenchlorophos and fenchlorophos-oxon)	0.1
Fenitrothion	0.5
Fenpropathrin	0.03
Fensulfothion (sum of fensulfothion, fensulfothion-oxon, fensulfothion-oxon sulfone, and fensulfothion sulfone)	0.05
Fenthion (sum of fenthion, fenthion-oxon, fenthion-oxon sulfone, fenthion-oxon sulfoxide, fenthion sulfone, and fenthion-sulfoxide)	0.05
Fenvalerate	1.5
Flucythrinate	0.05
τ-Fluvalinate	0.05
Fonophos	0.05
Heptachlor (sum of heptachlor, *cis*-heptachlorepoxide, and *trans*-heptachlorepoxide)	0.05
Hexachlorbenzene	0.1
Hexachlorocyclohexane (sum of isomers α-, β -, δ-, and ε-)	0.3
Lindan (γ-hexachlorocyclohexane)	0.6
Malathion and malaoxon (sum of)	1
Mecarbam	0.05
Methacriphos	0.05
Methamidophos	0.05
Methidathion	0.2
Methoxychlor	0.05

Pesticide limits in chapter <561> (contd.)

Mirex	0.01
Monocrotophos	0.1
Parathion-ethyl and paraoxon-ethyl (sum of)	0.5
Parathion-methyl and paraoxon-methyl (sum of)	0.2
Pendimethalin	0.1
Pentachloranisole	0.01
Permethrin and isomers (sum of)	1
Phosalone	0.1
Phosmet	0.05
Piperonyl butoxide	3
Pirimiphos-ethyl	0.05
Pirimiphos-methyl (sum of pirimiphos-methyl and *N*-desethyl-pirimiphos-methyl)	4
Procymidone	0.1
Profenophos	0.1
Prothiophos	0.05
Pyrethrum (sum of cinerin I, cinerin II, jasmolin I, jasmolin II, pyrethrin I, and pyrethrin II)	3
Quinalphos	0.05
Quintozene (sum of quintozene, pentachloraniline, and methyl pentachlorphenyl sulfide)	1
S-421	0.02
Tecnazene	0.05
Tetradifon	0.3
Vinclozolin	0.4

<561> Articles of Botanical Origin – Analytical methods

- SANCO/12571/2013 and its updated versions
- EPA method validation principles (OPPTS 860.1340)
  - Sample prep: suitable for the combination of pesticide residue and the matrix
  - LOQ: NMT tolerance limit
  - Recovery 70% - 120%
  - Repeatability NLT 20% RSD
  - Linearity

U.S. Regulatory Framework

- **Environmental Protection Agency** (EPA): 40 CFR Part 180 Tolerances and Exemptions from Tolerances for Pesticide Chemicals in Food.

- **Food and Drug Administration** (FDA): 21 CFR Part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements:
  - Specifications are required to ensure that a dietary supplement derived from a botanical source does not contain contaminants.
  - FDA samples individual lots of domestically produced and imported botanicals **and analyzes them for pesticide residues** to enforce the tolerances established by EPA.

U.S. Regulatory Framework

- **United States Department of Agriculture** (USDA): 7 CFR 205 National Organic Program Section §205.671 Exclusion from organic sale:
  - When residue testing detects prohibited substances in certified organic botanicals at levels that are greater than 5% of the EPA-tolerance for the specific residue detected or unavoidable residual environmental contamination, the agricultural product must not be sold, labeled, or represented as organically produced.
  - In the case of certified organic botanicals, the 5% rule provides no relief. Five percent of a zero value is still zero.

U.S. Regulatory Framework

- **United States Pharmacopeia (USP) <561>:** Within the U.S, many botanicals are treated as dietary supplements and are subject to the statutory provisions that govern foods but not drugs in the FFDCA. Limits for pesticides for foods are determined by the EPA, and where no limit is set, the limit is zero.
  - USP limits, therefore, are not applicable in the U.S. when articles of botanical origin are labeled for food or dietary supplement purposes.
  - USP limits are presently applicable in the U.S. only when the article an active ingredient of an OTC drug product (e.g., Psyllium Husk USP) or of a prescription botanical drug (e.g., Digitalis USP).
  - USP limits are applicable however to botanicals being used as ingredients of licensed or registered products in other countries where the *USP–NF* is recognized as Official Compendia (e.g., Listed Complementary Medicines in Australia or Licensed Natural Health Products in Canada, among others).

Most Botanicals Lack EPA Tolerances

- EPA pesticide tolerances are established on a species-specific and/or crop-group basis.
  - Pesticide tolerances have been established for only a relatively small number of cultivated botanical crops such as certain aromatic or culinary herbs (EPA Crop Group 19) that are cultivated in the U.S. on a large scale, e.g., spearmint tops (*Mentha spicata)*, as well as a few important economic herb crops like hop cones (strobiles) (*Humulus lupulus*) used mainly in beer production.
  - Yet no EPA tolerances have been established for many of the most important botanical crops in global commerce, for example no tolerances have been established for German chamomile flower (*Matricaria recutita*) which is cultivated (conventionally and organically) in several countries on several continents for export to the U.S.