



Global Expertise
Trusted Standards
Improved Health

USP Pesticide Roundtable: Collaboration Model

Josef A. Brinckmann

**USP Dietary Supplements Stakeholder Forum
Wednesday, June 7, 2017**

- ❑ **Multi-stakeholder consultations regarding U.S. pesticide limits as a model collaboration effort:**
 - ❑ **March 2016: USP Stimuli Article main points**
 - ❑ **May 2016: Public comment deadline - responses**
 - ❑ **Dec 2016 USP Roundtable with government & industry**
 - ❑ **Stakeholder engagement informs DSHM-EC on industry needs and challenges**
 - ❑ **2017: Post-roundtable developments**
- ❑ **Potential solutions and the way forward**

March 2016: USP Stimuli Article for Public Comment

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Need for Clear Regulation of Pesticide Residue Limits for Articles of Botanical Origin

Botanical Dietary Supplements and Herbal Medicines Expert Committee,^a and USP Staff^{a,b}

ABSTRACT *Articles of Botanical Origin* (561) provides limits for common contaminants, including pesticides, aflatoxins, and elemental impurities. The *USP* limits for pesticides specified in this chapter are applicable to botanical drugs, but since dietary supplements (DS) in the United States are regulated as a subset of foods, the U.S. limits for pesticides in botanical DS are set to the same levels as those for food by the Environmental Protection Agency (EPA), or the Food and Drug Administration (FDA) action levels determined on a case-by-case basis.

This creates a divide between two different standards for the same article of botanical origin, which results from the unintended consequences of U.S. regulations initially established for food crops, but now also applicable to botanical ingredients that fall within the DS regulatory framework. In the absence of EPA-established limits for an article, compliance with the *USP* limits is permitted for drugs, whereas zero tolerance is applied when the same ingredient is labeled as a food or as a DS.

The intent of this *Stimuli* article is to provide background about the need for rational limits for pesticides, to ensure the quality of articles of botanical origin, engage the stakeholders to strengthen *USP* standards with regard to contaminants, and solicit public comments that will be reviewed and considered by USP's Botanical Dietary Supplements and Herbal Medicines Expert Committee. It is recommended that *USP*-specified limits for DS be adopted as part of the Good Manufacturing Practices for Dietary Supplements in 21 CFR 111.

- ❑ Articles from an estimated 3,000 botanical species are in commerce **yet the majority of species have no EPA-established tolerances**. The majority of species are also wild-collected (not farmed) and therefore unlikely to ever have pesticide tolerance levels established.
- ❑ Residues of “legacy” (e.g. DDT) and “current use pesticides” (CUPs) now detected in Arctic ice caps (**evidence of long range atmospheric transport**).
- ❑ In rural areas, there is **widespread contamination of wildflowers** and bee-collected pollen with agricultural pesticides.
- ❑ **Nonpoint source pesticide detection** is an increasing problem even with certified organically grown and/or wild-collected botanicals.
- ❑ In the absence of EPA-tolerances, residues of “allowed pesticides” intentionally applied to conventional herb crops in other countries are “**unlawful pesticides**” as per FDA regulations (regulated as zero tolerance).

- ❑ **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 (OTC and Rx) but not to botanical dietary supplements, even when same botanical can be a drug or supplement (unless the dietary supplement label claims compliance with USP standards).
- ❑ **USDA** National Organic Program (NOP) permits not more than 5% of the EPA-tolerance for the specific residue detected or unavoidable residual environmental contamination. Because most botanical articles have no EPA-established tolerances, five percent of a zero value is still zero!!

USP received positive responses to the Stimuli Article from different types of stakeholders including:

- ❑ Accredited laboratories for analysis of botanical substances & products
- ❑ American and European processors and suppliers of botanical raw materials
- ❑ Manufacturers of botanical extracts
- ❑ Multinational manufacturers of botanical drug and botanical dietary supplement products

Comments strongly supported the proposal that USP limits for pesticide residues should be accepted broadly for all articles of botanical origin in the United States. Additionally, it was suggested that there should be a general MRL established for pesticides not listed in the pharmacopeia.

Furthermore, commenters urged harmonization of pesticide residue limits for articles of botanical origin among governments and pharmacopeias.

The Supplement

Quality Leadership

USP Roundtable on Pesticide Residues in Dietary Supplements

December 7, 2016

Good Manufacturing Practices for Dietary Supplements require manufacturers to control contaminants, but do not set out specific methods or maximum residue limits for pesticides. Since dietary supplements (DS) in the United States are regulated as a subset of foods, the U.S. limits for pesticides in botanical dietary supplements are set to the same levels as those for food crops by the Environmental Protection Agency (EPA). Although EPA establishes pesticide limits, the U.S. Food and Drug Administration (FDA) is responsible for enforcing them.:

USP General Chapter <561> *Articles of Botanical Origin* provides limits for common contaminants, including pesticides, aflatoxins, and elemental impurities, but compliance with USP limits is sufficient for botanical drugs, and not when the same ingredient is labeled for use as a dietary supplement. USP published a **Stimuli article** (*Pharmacopeial Forum* 42(2) March 1, 2016) to provide background about the need for rational limits for pesticides, to ensure the quality of articles of botanical origin, engage the stakeholders to strengthen USP standards with regard to contaminants, and solicit public comments that will be reviewed and considered by USP's Botanical Dietary Supplements and Herbal Medicines Expert Committee.

Following upon the comments for the Stimuli article, USP also organized a roundtable discussion with stakeholders on December 7, 2016, with the specific goal of exploring science-based solutions to the issue of pesticide residues in botanical dietary ingredients and dietary supplements in the majority of cases where EPA tolerances have not been established. Stakeholder input was collected on complex issues related to the regulatory requirements, experiences with USDA's 5% of EPA tolerances for organic crops, toxicological basis for crop specific pesticide limits, non-point source pesticide contamination of wild crops, risk-based testing, analytical method challenges, and harmonization across pharmacopeias. Participants included governmental policy makers and regulators (FDA, EPA, USDA National Organic Standards Board (NOSB), Health Canada, Canadian Food Inspection Agency), independent laboratories, trade associations, botanical ingredient suppliers and manufacturers of botanical dietary supplement products and botanical drug products. The participants discussed the need for a science-based approach for establishing pesticide residue limits in botanical dietary supplements considering the challenges from the current paradigm of crop-specific limits, which have not been set by the EPA for most of the commonly used herbs of commerce.

Major outcomes from the roundtable:

- Non-point source pesticide contamination observed in organic crops as well as in wild-collected botanicals illustrates that a zero-tolerance approach is not rational, and that science-based standards could provide a framework to establish toxicologically sound limits.
- The current paradigm of crop-specific limits which have not been set by the EPA for most of the commonly used herbs in commerce should be corrected through science-based approaches such as the pharmacopeial standards of the USP and PhEur.

Products & Services

Standards Open for Public Comment Until May 31, 2017

The standards below were published for public comment on March 1, 2017, and will receive and consider feedback until March 31, 2017. To comment, please visit:
<http://www.usp.org/usp-nf/pharmacopeial-forum>.

New Monographs

- European Elder Berry Dry Extract
- Valerian Root Dry Extract Capsules
- Valerian Root Powder Capsules
- *Vitex negundo* Leaf
- *Vitex negundo* Leaf Powder
- *Vitex negundo* Leaf Powder Leaf Dry Extract
- Calcium Citrate Malate
- Carotenes
- Cholecalciferol Tablets

Revised Monographs

- Powdered Decaffeinated Green Tea Extract
- Flax Seed Oil

Main outcomes: USP Pesticide Roundtable

- ❑ **Nonpoint source pesticide contamination** of organic botanical crops as well as wild-collected botanicals illustrates that a zero-tolerance approach is not rational, and that science-based standards could provide a framework to establish toxicologically sound limits.
- ❑ **A survey** should be carried out to determine the magnitude of concern from nonpoint source pesticides observations and published in order to increase awareness amongst the regulators.
- ❑ **Science-based approach:** The current paradigm of crop-specific limits which have not been set by the EPA for most herbs of commerce should be corrected through science-based approaches such as the pharmacopeial standards of the USP and PhEur.
- ❑ **Toxicological basis:** Participants contrasted the toxicological basis for controlling exposure to contaminants such as lead and residual solvents (irrespective of the exposure source) with the crop-specific basis for controlling pesticide residue exposure..

Main outcomes: USP Pesticide Roundtable

- ❑ **Legal Recognition of USP Standards:** Participants suggested that EPA or FDA incorporate *USP–NF* by reference into regulations as an acceptable compendium for determining pesticide residue contaminants on all articles of botanical origin. .
- ❑ **It's not so easy!** Understanding the challenges of regulatory amendments, inclusion in FDA guidance of USP pesticide residue limits as action levels in the absence of a specific MRL was also discussed.
- ❑ **Contaminant or additive?** An FDA attendee suggested that pesticide residues detected on a botanical that is certified organically grown or wild collected could be considered to be a **contaminant rather than an additive**. EPA tolerances are applicable to specific crops where the pesticide chemical has been intentionally applied. Regulators could view nonpoint source pesticide contamination of wild crops differently than detection of crop-specific pesticide residues within EPA-established tolerances.

Main outcomes: USP Pesticide Roundtable

- ❑ **Import refusals:** Case studies of FDA enforcement actions that have been taken based on zero tolerance illustrated the impact to the industry and international commerce.
- ❑ **Analytical challenges:** Establishing limits involves consideration of analytical method challenges related to complex botanical matrices, and harmonization across pharmacopeias to facilitate international commerce.
- ❑ **How about a general MRL?** Participants suggested adoption of a general MRL for limiting pesticide residues for which EPA or USP limits are not set, similar to the Canadian general MRL of 0.1 ppm.
- ❑ **Trace levels requiring no action?** FDA Compliance Program Guidance Manual (CPG): Pesticides and Chemical Contaminants in Domestic and Imported Foods-CP7304.004 - It is worth examining whether Lab Class "2" results (residue with no established tolerance or guideline detected but at a trace level requiring no follow-up) provide regulatory relief. "Trace level" is defined as a residue above the LoD but below the LoQ, which is still specific to the analytical method!!

Stakeholder engagement informs DSHM-EC on industry needs and challenges

Comments received from the stimuli article and comments made at the roundtable have informed the work program of the DSHM-EC. As a result:

- ❑ USP Scientific Staff and EC Members have prioritized attending and presenting on the topic at relevant conferences.
- ❑ USP committed to hold meetings with EPA, FDA, USDA, NOSB and others to advocate for USP standards as a part of the solution.
- ❑ USP may potentially revise the pesticide list, limits and methods section in the USP General Chapter <561> Articles of Botanical Origin.
- ❑ USP aims to collect information on nonpoint source contamination from botanical companies, trade associations, and through proposed collaborations with other pharmacopeias.
- ❑ The EC will develop a manuscript that quantifies the problem of nonpoint source pesticide contamination, with an argument for legal recognition of USP standards, targeted for 2018 publication in the **Food and Drug Law Journal**

One outcome of the roundtable was in the form of invitations to participate in professional conferences:

- ❑ **The Toxicology Forum**, Washington, DC (Feb, 2017)



- ❑ **International Conference on the Science of Botanicals**, Oxford, MS (April, 2017)



- ❑ **MRL Workshop**, San Francisco, CA (May, 2017)



2017 MRL Harmonization Workshop
May 31 & June 1, 2017
San Francisco, CA

6/9/2017

Quirks in regulations create need for science-based pesticide limits, USP says



Breaking News on Supplements, Health & Nutrition - North America

Quirks in regulations create need for science-based pesticide limits, USP says

By Hank Schultz, 06-Apr-2017

Related topics: Regulation, Supply Chain Management, Regulations, Legislation & Enforcement

Quirks of regulatory policy regarding pesticides leave botanical dietary supplement ingredients subject to unwarranted seizure, attendees at an international botanical conference in Mississippi were told.

In a session at the 17th Annual Conference on the Science of Botanicals taking place in Oxford MS this week, Nandakumara Sarma PhD director of dietary supplements at USP, said the way pesticide regulations are written in the United States, many botanical ingredients are in the untenable position of being subject to import seizure if even trace amounts of certain pesticides can be detected in the lot. In other words, for some pesticides when found in certain botanical materials meant for dietary supplements, there is a zero tolerance policy, even if those same pesticides are allowed at higher (but still low) levels on lots of material meant to be consumed as food.

Intentional vs unintentional

Sarma said the issue came about this way: Pesticide regulations in the U.S. have been promulgated by the Environmental Protection Agency and pertain to known risks from pesticides applied to food crops. The verb is important in that sentence, as these regulations only cover intentional applications, and were written on a crop-by-crop basis. But Sarma said some of the underlying principles behind the legislation no longer hold true. The underlying assumption was that if a detectable amount of a pesticide showed up on a crop, it got there because the farmer put it there. If there is no specified level for that pesticide in a given crop, the tolerance level automatically reverts to zero.

But pesticides have been in wide scale use around the globe for seventy years or so now, and many of these chemicals, especially the older, legacy pesticides, were engineered to be persistent in the environment. Pesticide residues have been detected in alpine snow fields and Antarctic ice. As a result, Sarma said, finding places in the world where crops can be grown or botanicals can be wild harvested without at least trace amounts of unwanted pesticides showing up is becoming nigh on impossible. This issue is coupled with the fact that analytical methods have advanced, and ever lower detection limits are possible. This is of particular concern for wildcrafted items, which make up a large proportion of the trade in botanical dietary supplement ingredients. The global wildcrafted botanical ingredient supply chain we know today was really a tiny niche market activity when the principles underlying the pesticide rules were put into place, Sarma said.

"In wild harvest, no EPA pesticide levels were ever established for these crops," Sarma said.

Need for science-based limits

Sarma said the intended use of the item also changes the allowable pesticide limits, giving rise to situations that make no objective sense. For example, the pesticide tricyclazole is allowed at 3 ppm on rice. But as there is no level established for this pesticide in a botanical dietary ingredient that would go into a supplement, it may not be present at any level in that material, even though a consumer could be expected to consume hundreds of times more of the rice by volume in a day.

The intended use of the item—or, put another way, the sales category of the finished product—can affect the pesticide tolerances on the same ingredient, too, Sarma said. For example, one tolerance level applies to psyllium seed husk when used in an OTC bulking laxative, and another when it is sold as a dietary ingredient for dietary supplement use, even if the dosage is the same in both cases. Sarma showed attendees two slides listing more than 30 common botanical dietary ingredients. Of these only five had EPA pesticide limits associated with them.

Sarma said USP is engaging in roundtable discussion with EPA, FDA, USDA's Organic Standards Board, Health Canada and others to address the issue. The goal is not to give industry an "out," but rather to rationalize and harmonize the regulations along risk-based and science-backed lines.

"The supply chain is really global. We live in a contaminated world, and while we want the pesticide levels to be as low as possible, we are trying to address the gaps in the regulations," Sarma said.

In addition to the Oxford meeting, Sarma recently presented the issue at a meeting of the Toxicology Forum in Washington, DC and will present it again next month at a workshop in San Francisco put on by the California Specialty Crops Council. To read USP's original stimulus article on the subject, [click here](#).

The Oxford conference, put on by the National Center for Natural Products Research at the University of Mississippi, began on Monday and wraps up today. For more information on the conference, [click here](#).

<http://www.nutraingredients-usa.com/content/view/print/1390786>

1/2

USP DSHM-EC viewpoint:

- ❑ Achieving legal recognition by FDA in 21 CFR of the USP (561) limits, applied broadly to all herbs of commerce, **would solve (most of) the problem** in terms of quality assurance, safety and the ability of industry to procure botanical raw materials without risk of import refusals (due to absence of EPA tolerances).
- ❑ However, USDA NOP 7 CFR § 205.671 (“Exclusion from organic sale”) would also need to reference USP limits **in order to solve most of the problems**.
- ❑ Amending USP General Chapter (561) limits to add a gMRL for pesticides not listed in Table 4 that also lack EPA tolerances and/or FAO-WHO limits would also help as well as collaboration with other pharmacopeias to harmonize pesticide residue limits.

EPA current thinking:

At the 2017 MRL Workshop, Rick Keigwin, Acting Director, OPP, EPA, elaborated 4 international involvement goals:

1. Strengthen Protections – food safety, **facilitate trade**, environmental protection;
2. **Enhance Regulatory Decisions through Collaboration** – improve science base and enhance regulatory efficiency;
3. Conserve Resources – the availability of resources for governmental agencies is dwindling;
4. **Minimize Barriers** – make sure that setting of MRLs are set in a way that does not result on trade barriers.

EPA current thinking:

At the 2017 MRL Workshop Mr. Keigwin also suggested new areas of potential flexibility to explore, in particular:

In a pilot project, EPA may consider incorporating international Codex limits in cases where no EPA-established tolerances exist.

Q.: In that case, could EPA also consider incorporating the official USP limits?

EPA could consider viewing “inadvertent residues” as contaminants, rather than as residues of intentionally applied pesticides.

Q. In that case, would nonpoint source pesticide contamination (inadvertent residues) detected on wild collected or organic herbs still be subject to FDA enforcement of the EPA tolerances that are established for intentional application on specific food crops?

Trade association viewpoints:

AHPA (American Herbal Products Association):

In May 2017, AHPA submitted comments in response to EPA's "**Request for Comments on Evaluation of Existing Regulations**" recommending that EPA should continue to expand Crop Group 19 [referring to the IR-4 (**Interregional Research Project No. 4**)]; should create exceptions for unavoidable, inadvertent pesticide residues; should create general tolerances for pesticides intentionally applied in foreign countries; should use Codex Alimentarius Commission MRLs and scientific evaluations.

ASTA (American Spice Trade Association):

At the 2017 MRL Workshop, John Hallagan, General Council, ASTA, stated that ASTA has worked to add MRLs for spices through the Codex process. ASTA is also discussing the use of Codex MRLs with EPA in cases where no EPA-established tolerance exists. ASTA also supports expanding the IR-4 Project crop grouping approach.



Global Expertise
Trusted Standards
Improved Health

www.usp.org

Thank You