In Food & Agriculture, We Set the Standard

Voluntary Consensus Standard for the Determination of Pyrrolizidine Alkaloids in Teas, Herbal Infusions, and other Foods Containing Herbal Ingredients

AOAC 2021 Initiative

AOAC INTERNATIONAL is proposing the establishment of a working group to develop a voluntary consensus standard (or standards) for the determination (quantification) of 35 pyrrolizidine alkaloids (PAs) (comprising 21 PAs of regulatory importance and 14 others known to co-elute with one or more of the identified 21 PAs) in teas, herbal infusions, herbs, seed spices and botanical dietary supplement ingredients to meet new maximum levels (MLs) recently adopted through the European Commission Regulation (EU) 2020/2040[1]. The Working Group will develop one or more Standard Method Performance Requirements®, or SMPRs® (as deemed necessary by WG experts), based on priorities established by the project's Advisory Panel (see below). The standards adopted through this working group will provide the analytical basis for the development of new testing methods that will:

- Substantiate the effectiveness of good agricultural collection practices,
- Support regulatory compliance and surveillance programs, i.e. monitor prevalence of PAs in raw agricultural commodities and finished botanical products, and
- Support prevention measures and minimize the risk for importers, exporters and finished product producers.

Background

Pyrrolizidine alkaloids (PAs) are secondary plant metabolites consisting of a necine base and 1 or 2 necic acids (esterifying acid). PAs can be open-chain mono- or diesters or macrocyclic diesters. They can be present in plants as free base or as N-oxides. PAs and their associated N-oxides are produced by an estimated 6000 plant species (about 3% of the world's flowering plants) and are thought to act as a defense mechanism against insect herbivores. PAs with certain structural features are hepatotoxic and genotoxic carcinogens.

The presence of detectable (measurable) levels of PAs throughout the food chain, e.g. in agricultural and minimally processed foods and food supplements, is of particular concern. In addition to their inherent presence in certain plants, accidental co-harvesting of PA-producing weeds is another significant contributing factor. PAs can be found in grain crops contaminated with PA containing weeds herbal products such as teas, liquid infusions, and other selected

botanicals and spices. They have also been detected in foods of animal origin (milk, honey, egg, offal) though in very low amounts (ppb). This is attributed to animal grazing on PA-producing plants or feeds.

In the United States, the U.S. Food and Drug Administration (US-FDA) since the early 2000s has taken the unofficial position for a zero-tolerance policy for PAs[2,3]. This position arose principally through concerns with the marketing of supplements that contain the herbal ingredient comfrey, as these plants are known sources of PA; and a recognition that these compounds present a considerable threat to human health. Regarding the establishment of maximum tolerance levels, the US-FDA took the position that no level of PA is acceptable and did not believe that there is adequate scientific evidence to establish an exposure level that would present no harm to consumers.

In contrast, the EU took a more measured and actionable approach over those years to keep levels of PAs in the food chain as low as reasonably achievable through guidance on good agricultural practices, periodically updated risk assessments on exposure estimates and consumption data in products susceptible to PA contamination. In December 2020, however, Commission Regulation (EU) 2020/2040[1] finally established maximum levels (MLs) for the sum of 35 PAs in teas, herbal infusions (including those for infants and young children), pollen and pollen products, and other food and dietary commodities.

Of those PAs characterized and of toxicological relevance, 21 occur in quantifiable amounts. These are the focus for the newly established EU MLs and present a new challenge analytically. To date, two laboratory testing approaches (sum parameter analysis and targeted analysis) are employed for the quantification of these PAs in commodities of importance. Each consists of a complex multi-step protocol for sampling, sample preparation and LC-MS/MS analysis; and are based on the quantified sum of these 21 analytes. However, accurate quantification for regulatory purposes using current testing paradigms may not always be possible. Fourteen (14) additional, naturally occurring isomers display chromatographic patterns (by LC retention times and MS fragmentation) that are indistinguishable by currently available methodologies. Similarly, the ratio of PA forms (PA-*N*-oxide and its free tertiary base) create uncertainty in accurate ML quantification.

Seeking Support

The Pyrrolizidine Alkaloids Advisory Panel will be comprised of funding organizations to determine initial priorities and working group strategies. This panel will meet quarterly to review progress and consider additional objectives based on working group accomplishments and any new challenges that may arise. The projected funding level needed to complete this initiative as described is $80,000 (see Appendix 1 for services provided). We are asking organizations to join this important project for a contribution of $10,000. Other levels of contributions will be considered as well[*].

Benefits for You

Method developers

- Influence the development of consensus standards, which will be used by AOAC Expert Review Panels to evaluate your candidate methods for possible adoption as AOAC Official Methods of Analysis.
- AOAC Official Methods of Analysis will be the benchmark for trade resolutions, instill consumer confidence, and contribute to consumer safety.

Food manufacturers or food distributors:

- Ensure that project priorities meet your needs through AOAC INTERNATIONAL's unique standard development process,
- Encourage the development of *Official Methods* which provide the highest level of analytical confidence for authenticity claims and detect fraudulent adulteration in priority commodities,
- Provide a validated analytical means needed to meet regional and internationally adopted regulatory requirements,
- Protect producers and consumers alike, maintain the reputation of products and ultimately improve the quality and safety of the food supply, i.e. substantiate the effectiveness of good agricultural collection practices, and support prevention measures and minimize the risk for importers, exporters and finished product producers.

For all:

- Create much-needed reference methods for PAs of regulatory importance in commodities that do not currently exist,
- Generate reliable data for effective compliance-driven quality control of food materials and products, i.e. through regulatory compliance and surveillance programs designed to monitor prevalence of PAs in raw agricultural commodities and finished botanical products.

**AOAC will continue to explore a multi-tiered funding schedule to avoid any unintended barrier to the ultimate success of this project and to encourage as many stakeholders to get involved as possible.*

CONTACT INFORMATION

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References

[1] Commission Regulation (EU) 2020/2040 of 11 December 2020 amending Regulation (EC) No 1881/2006 as regards maximum levels of pyrrolizidine alkaloids in certain foodstuffs
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R2040&from=EN

[2] https://wayback.archive-it.org/7993/20170722025637/https://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/ucm111219.htm

APPENDIX 1

The base fee per Working Group is <u>$80,000</u> USD and includes:

- ***Advisory Panel Meetings****. AOAC will hold an Advisory Panel Meeting to identify renowned subject matter experts and to identify additional key authorities and experts to participate on AOAC working groups.*
- ***AOAC Stakeholder Meeting****. Working Group Chairs will present the Working Group launch presentation and the stakeholders will refine fitness for purpose.*
- ***AOAC Working Group Meetings****. The Working Groups will hold a series of teleconferences, as needed, to complete the draft SMPR(s).*
- ***AOAC Stakeholder Meeting****. Working Group Chairs will present draft SMPRs for approval by the stakeholders. Stakeholders will deliberate and reach consensus on and thereby approve a final version of the SMPR(s).*
- ***Publication Costs.*** *SMPR(s) approved by the stakeholder community will be published in A*OAC venues (i.e., *Official Methods of Analysis of AOAC INTERNATIONAL* and AOAC Website).
- ***Training and education materials/webinar(s) for method developers.***

Additional Fees (as applicable):

1. Application Fees for *Official Methods*^{SM} Review - $35,000 USD per method[1]:
   - Includes recruitment of Expert Review Panel (ERP) Members (Volunteer Experts),
   - Includes Preparation and Review of Methods for Review,
   - Includes ERP Orientation and Facilitating ERP Meetings,
     - Initial in-person meeting and, if methods are adopted, maintenance of ERP over the two (2) year method tracking period,
   - Includes ERP review of Method Modifications during the 2-year tracking period,
   - Includes Publications of methods and method manuscripts.

2. Application Fees for Modifying or Extending an Official Method of Analysis - $10,000 per method:
   - Includes Preparation and Review of Methods for Review,
   - Includes ERP Orientation and Facilitating ERP Meetings,
     - Initial in-person meeting and if methods are adopted, maintenance of ERP over the two (2) year method tracking period,
   - Includes ERP review of method during the 2-year tracking period, if required
   - Includes Publications of methods and method manuscripts.

Optional Enhancements (per method):

[1] Base application fee. AOAC Organizational Member discounts may apply.

- Consultation on validation test protocols: $3,000 USD
- Drafting Protocols & Review of Protocol: $3,000 USD
- Drafting of Method in AOAC Format: $2,000 USD
- Drafting of Method Manuscript in AOAC Format: $5,000 USD

NOTE: Travel costs of ERP members and coordination of laboratory work if needed are not covered. New application fees for resubmission will be required if an ERP does not approve the initial method submission.