Cannabis Analytical Science Program

The Four Pillars of Quality Measurement: Standards, Validated Methods, Proficiency Testing, & Training

Scott Coates

Senior Director

AOAC Research Institute

AOAC INTERNATIONAL

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AOAC INTERNATIONAL — Who are we?

- Independent non-profit 503 (c)
- About 40 staff
- About 4,000 members
  - Chemists
  - Microbiologists
  - Molecular biologists
- 16 regional sections
  - US
  - Europe
  - Asia
  - Africa
  - South America

AOAC INTERNATIONAL — At a Glance

AOAC's history is intertwined with the development of food safety science in the US:

- Formed in 1884 at USDA, later part of FDA, AOAC became independent in 1970s
- ***Official Methods of Analysis***
- **Standards Development**
- Laboratory Proficiency Testing Program

- Consensus Builder
- Global Trade Facilitator
- International Member Base
- Academic, Industry & Regulatory Collaboration.

AOAC INTERNATIONAL Programs

- Stakeholder Panel on Infant Formula and Adult Nutritionals (SPIFAN)
- Stakeholder Panel on Agent Detection Assays (SPADA)
- Stakeholder Panel on Dietary Supplements (SPDS)
- International Stakeholder Panel on Alternative Methods (ISPAM)

NEW

- Analytical International Methods and Standards (AIMS)
- Food Authenticity & Fraud Program (FAFP)
- Cannabis Analytical Science Program (CASP)
- Emergency Response Validation for Corona Virus

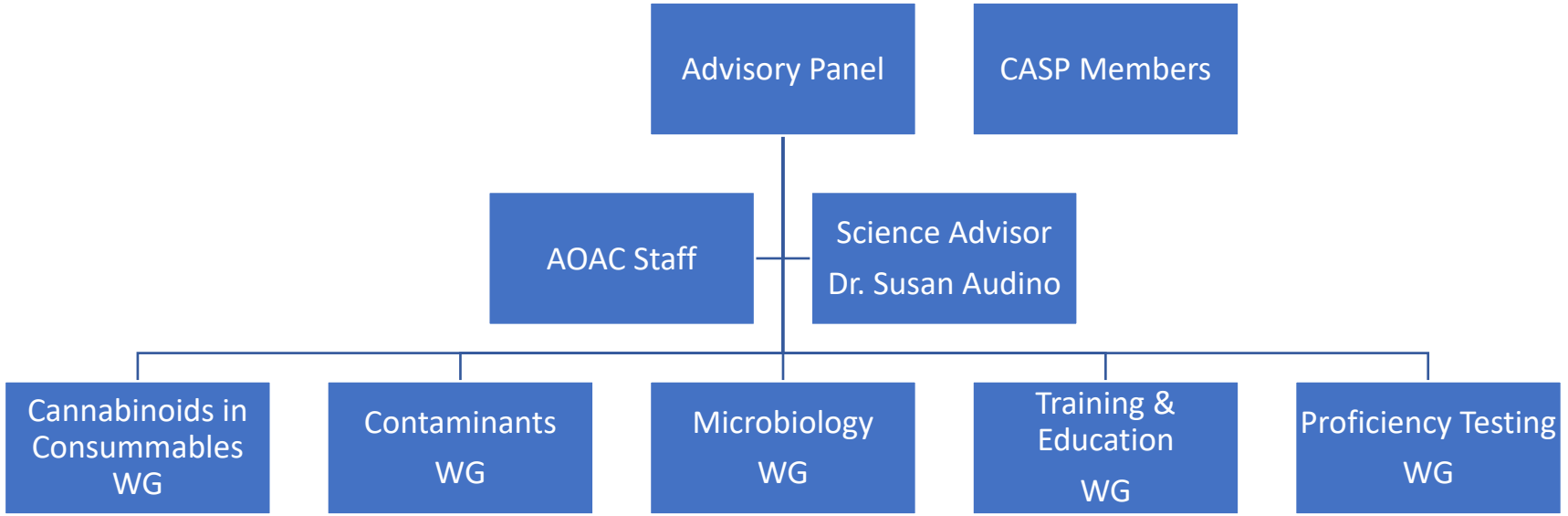
Cannabis Analytical Science Program (CASP)

- AOAC decided to create a full-time, dedicated program to cannabis analytical science in 2018.
- CASP to include all of AOAC's programs:
  - Official Methods of Analysis
  - *Performance Tested Methods*
  - *Standard Method Performance Requirements*
  - Laboratory Proficiency Testing
  - Publications *(Journal)*
  - Meetings

CASP Objectives

- Facilitate a forum where the science of cannabis analysis is discussed with international experts.
- Facilitate the development and publication of cannabis and hemp-specific methods and standards.
- Develop cannabis and hemp reference materials.
- Establish a cannabis and hemp proficiency testing program in accord with International Standards.
- Provide analytical and laboratory management training, in particular ISO accreditation training.
- Provide resources and education to regulators responsible for establishing rules and laws around cannabis and hemp.

CASP Organization



CASP Advisory Panel

Pioneer		
AFDO	SōRSE Technology	TEQ Labs
Titan Analytical	GW Pharma	PerkinElmer
Bio-Rad	Applied Food Sciences	R-Biopharm
MilliporeSigma	Ionization Labs	Supra R&D
ABC Testing	Materia Medica Laboratories	

Partner		
CV Sciences	Eurofins Scientific	

Affiliate		
Alkemist Laboratories	CEM Corporation	Crystal Diagnostics
IFT	Canopy Growth Corporation	BIOTECON Diagnostics
Hygeina	SC Labs	Medicinal Genomics
Charm Sciences		

Four Pillars

Standards

AOAC Standard Methods Performance Requirements

Validated Methods

Performance Tested Methods (PTM)

Official Methods of Analysis (OMA)

Proficiency Testing

AOAC Laboratory Proficiency Testing Program

Training

AOAC Method Validation Training Course

Standard Methods Performance Requirements

- commonly called an “SMPR”.
- documents a community’s analytical method needs.
- very detailed description of the analytical requirements.
- includes method acceptance requirements.
- published as a standard.
- unique to AOAC.

Standard Methods Performance Requirements

- Basis for method acceptance and approval.
- Guidance to method developers for the development of new methods.
- Advance the state-of-the-art in a particular direction.
- Address specific analytical needs.

SMPR Components

1. Purpose
2. Applicability
3. Analytical Technique
4. Definitions
5. Method Performance Requirements
6. System Suitability
7. Reference Materials
8. Validation Guidance
9. Maximum Time to Results
10. Tables

Method Performance Requirements (Quantitative)

- Analytical range
- Limit of detection
- Limit of Quantitation
- Repeatability
- Recovery
- Reproducibility

4. Method Performance Requirements

Analytical range	0.01–5.0[a]	
Limit of detection (LOD)	≤0.004[a]	
Limit of quantitation (LOQ)	≤0.01[a]	
Repeatability (RSD_r)	0.01[a]	≤15%
	0.2[a]	≤7%
	0.5[a]	
	5.0[a]	
Recovery	0.01[a]	90–110%
	0.2[a]	
	0.5[a]	
	5.0[a]	
Reproducibility (RSD_R)	0.3	≤11%
	0.6	
	1.0	
	2.5	
	5.0	
Concentrations apply to (*1*) "ready-to-feed" liquids "as is"; (*2*) reconstituted powders (25 g into 200 g water); and (*3*) liquid concentrates diluted 1:1 by weight.		
[a] µg/100 g expressed as cyanocobalamin in reconstituted final product.		

Method Performance Requiremments (Qualitative)

- Probability of Detection (POD)
- Acceptable Minimum Detection Level (AMDL)
- Inclusivity
- Exclusivity

AOAC SMPR® 2019.003

Standard Method Performance Requirements (SMPRs®) for Quantitation of Cannabinoids in Plant Materials of Hemp (Low THC Varieties *Cannabis* sp.)

Intended Use: Consensus-Based Reference Method

1 Purpose

AOAC SMPRs describe the minimum recommended performance characteristics to be used during the evaluation of a method. The evaluation may be an on-site verification, a single-laboratory validation, or a multi-site collaborative study. SMPRs are written and adopted by AOAC composed of representatives from the industry, regulatory organizations, contract laboratories, test kit manufacturers, and academic institutions. AOAC SMPRs are used by AOAC expert review panels in their evaluation of validation

Reproducibility.—Standard deviation or relative standard deviation calculated from among-laboratory data. Expressed as the reproducibility standard deviation (SD_R); or % reproducibility relative standard deviation ($\%RSD_R$).

Total THC.—Maximum potential percentage w/w delta-9-tetrahydrocannabinol that the test sample could yield on a dry weight basis, including delta-9-THC and delta-9-THCA.

5 Method Performance Requirements

See Tables 3 and 4.

6 System Suitability Tests and/or Analytical Quality Control

Suitable methods will include blank check samples, and check standards at the lowest point and midrange point of the analytical range.

A detailed description of the method's dry weight procedures and calculations must be included.

7 Reference Material(s)

See Tables 1 and 2 for sources of reference materials.

Refer to Annex E: *Development and Use of In-House Reference*

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Applicability

The method will be able to identify and quantify individual cannabinoids (as listed in Tables I and 2) in plant materials expressed on a dry weight basis. The method must be able to report total THC (as defined in this SMPR), regardless of how it is measured.

Table 1. Required cannabinoids

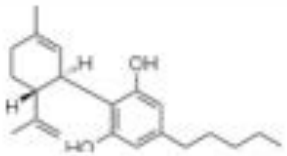
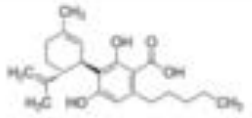
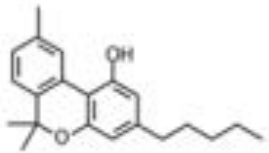
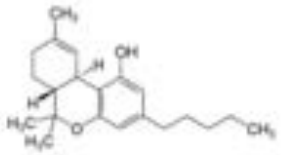
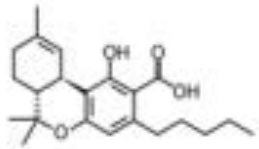
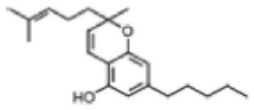
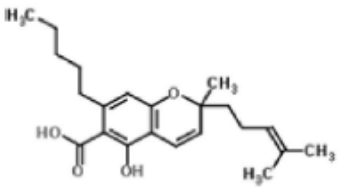
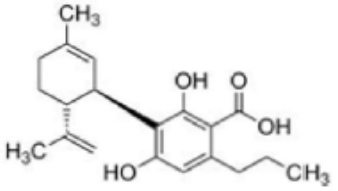
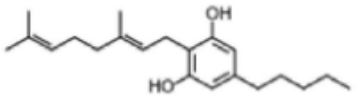
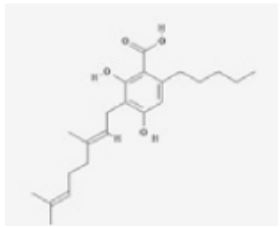
Common name	Abbreviation	IUPAC name	CAS No.	Molecular structure	Reference material
Cannabidiol	CBD	2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol	13956-29-1		Restek Cerilliant Sigma-Aldrich API Standards Echo Pharm Lipomed AG
Cannabidiolic acid	CBDA	2,4-Dihydroxy-3-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-6-pentylbenzoic acid	1244-58-2		Cerilliant USP Restek Lipomed AG Echo Pharmaceutical
Cannabinol	CBN	6,6,9-Trimethyl-3-pentyl-benzo[*c*]chromen-1-ol	521-35-7		Cerilliant Restek
Tetrahydro-cannabinol	THC	(−)-(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	1972-08-3		Cerilliant USP Echo Pharmaceuticals
Tetrahydro-cannabinolic acid	THCA	(6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6h-benzo[c]chromene-2-carboxylic acid	23978-85-0		Cerilliant USP Echo Pharmaceuticals

Table 2. Additional, desirable cannabinoids

Common name	Abbreviation	IUPAC name	CAS No.	Molecular structure	Reference material
Cannabichromene	CBC	2-Methyl-2-(4-methylpent-3-enyl)-7-pentyl-5-chromenol	20675-51-8		Cerilliant Sigma Aldrich Echo Pharmaceuticals
Cannabichromenic acid	CBCA	5-Hydroxy-2-methyl-2-(4-methyl-3-penten-1-yl)-7-pentyl-2*H*-chromene-6-carboxylic acid	20408-52-0		Cerilliant
Cannabidivarinic acid	CBDVA	2,4-Dihydroxy-3-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-6-propylbenzoic acid	31932-13-5		Cerilliant
Cannabigerol	CBG	2-[(2*E*)-3,7-dimethylocta-2,6-dienyl]-5-pentyl-benzene-1,3-diol NIST: 1,3-Benzenediol, 2-(3,7-dimethyl-2,6-octadienyl)-5-pentyl-	25654-31-3 NIST: 2808-33-5		Cerilliant Lipomed AG Echo Pharmaceuticals SPEX Certiprep Tocris (UK)
Cannabigerolic acid	CBGA	3-[(2*E*)-3,7-dimethylocta-2,6-dienyl]-2,4-dihydroxy-6-pentylbenzoic acid	25555-57-1		Cerilliant Echo Pharmaceuticals SPEX Certiprep

Nine more desirable cannabinoids for a total of 14 possible cannabinoids of interest.

Definitions

Total THC.- Maximum potential percentage w/w delta-9-tetrahydrocannabinol that the test sample could yield on a dry weight basis, including delta-9-THC and delta-9-THCA.

Table 3. Method performance requirements (part 1) for cannabinoids

Parameter	Requirement[a]
Limit of quantitation (LOQ), %	≤0.05
Analytical range (CBD and CBDA), %	0.05–35
Analytical range (others), %	0.05–5

[a] All calculated on dry weight basis.

Table 4. Method performance requirements (part 2) for cannabinoids

	Analytical range, %[a]		
Parameter	0.05–0.5	>0.5–5	5–35[b]
Recovery, %	85–118	90–111	95–105
RSD_r, %	≤5	≤3	≤2
RSD_R, %	≤10	≤8	≤6

[a] All calculated on dry weight basis; observed values to be compared to indicated limits for acceptability.

[b] Only applicable to CBD and CBDA.

Published Cannabis-Focused SMPRs

2017.001	**Quantitation of Cannabinoids in Cannabis Concentrates**
2017.002	**Quantitation of Cannabinoids in Dried Plant Materials**
2019.001	**Detection of Aspergillus in Cannabis and Cannabis Products**
2018.011	**Identification of Pesticide Residues in Dried Cannabis**
2019.002	**Identification of Selected Residual Solvents in Cannabis**
2019.003	**Quantitation of Cannabinoids in Plant Materials of Hemp**
2019.001	**Detection of Aspergillus in Cannabis and Cannabis Products**

Cannabis-Focused SMPRs Approved March 2020

Detection of Salmonella in Cannabis and Cannabis Products

Determination of Heavy Metals in a Variety of Cannabis and Cannabis-Derived Products

SMPRs In Process

Detection of Shiga Toxin Producing E. coli (STEC) in Cannabis Products

Determination of Heavy Metals in a Variety of Cannabis and Cannabis-Derived Products

Screening Method for Mycotoxins in Cannabis

Confirmation Method for Mycotoxins in Cannabis

Hemp Drying Procedure

Hemp Drying Procedure

The USDA AMS Interim Final Rule for the Domestic Hemp Production program program stipulates hemp to be delivered as is (not dried). Apparently there little consensus on drying temperature, times, and standard mass. The Cannabinoids working group is surveying the different drying procedures, and will try to develop a consensus standard procedure for drying.

Next Topics

Personal care products

Veterinary products

Terpenes

Vitamin E acetate (Vape products)

Listeria

Total yeast & molds

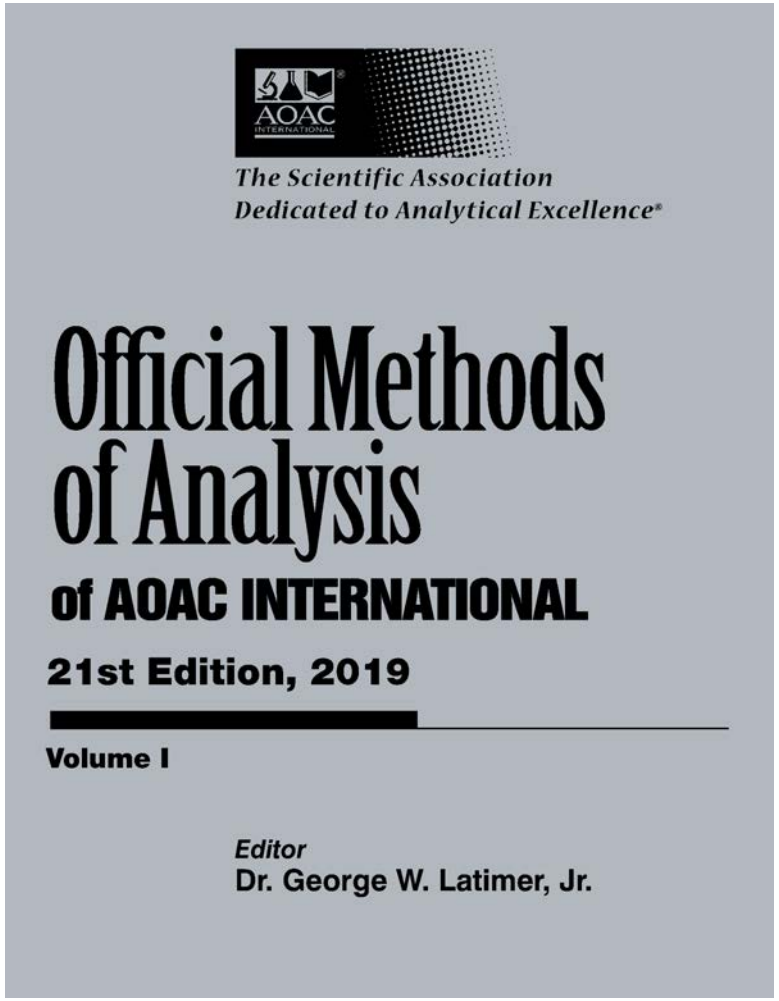
Second Pillar: Validated Methods

Official Methods of Analysis

Performance Tested Methods

Official Methods of Analysis

The ***Official Methods of Analysis*** is an international source of methods, in which scientists worldwide contribute their expertise to standards development, method development, and the systematic evaluation and review of methods. It is the most comprehensive collection of chemical and microbiological methods available in the world,



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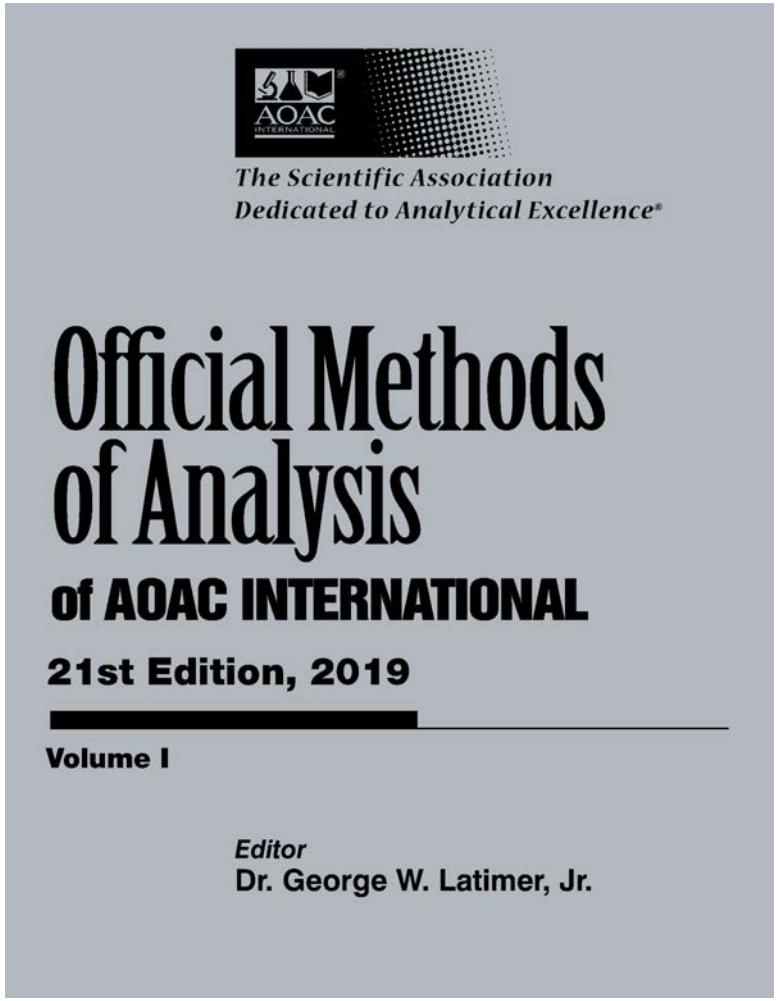
Official Methods of Analysis

- OMA methods are recognized in the U.S. Code of Federal Regulations and are legally defensible in courts worldwide.
- Many OMA methods have been adopted by the International Organization for Standardization (ISO).

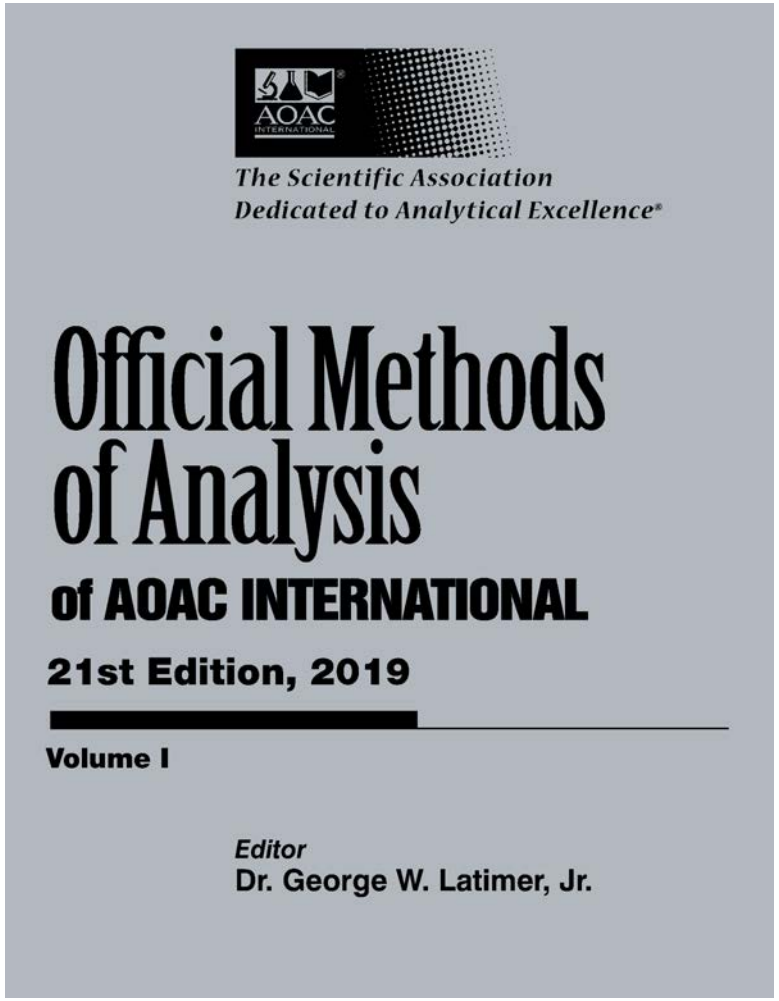


AOAC INTERNATIONAL

Official Methods of Analysis

The program evaluates:

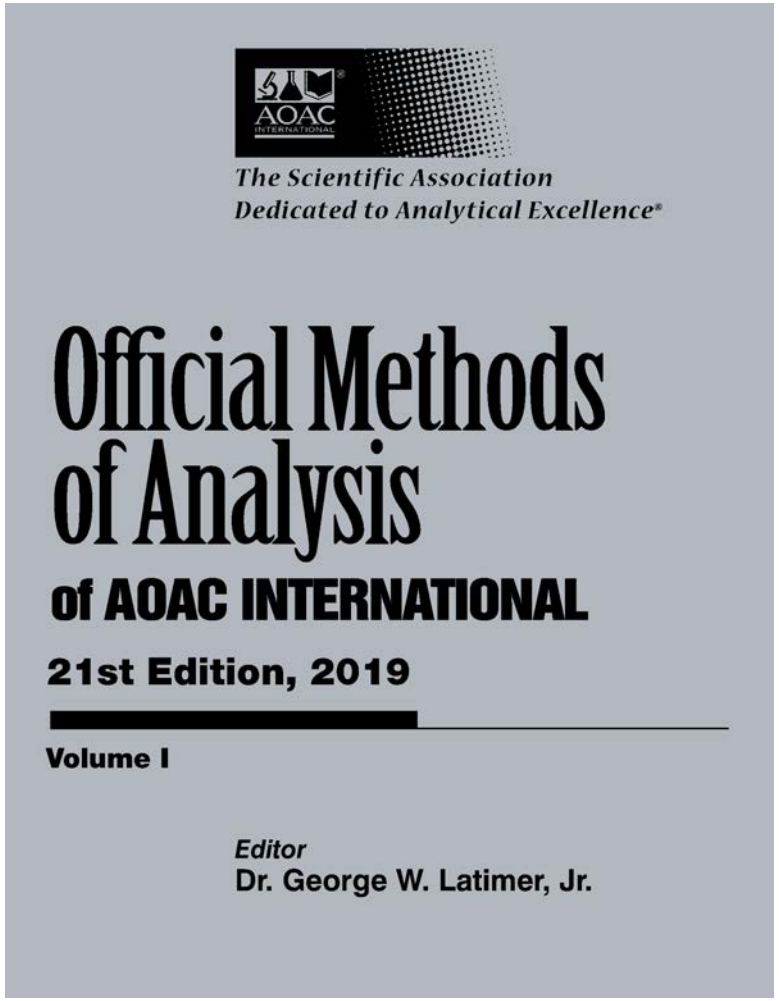
- Chemistry methods,
- Microbiology methods,
- Molecular biology methods,
- Traditional benchtop methods,
- Instrumental methods, and
- Proprietary, commercial, and/or alternative methods.



AOAC INTERNATIONAL

Official Methods of Analysis

- The hallmark of *Official Methods of Analysis* is the collaborative study.
- Common samples analyzed by multiple laboratories.
- Minimum of 8 laboratories reporting data.
- Accuracy, Reproducibility, and Repeatability determined.



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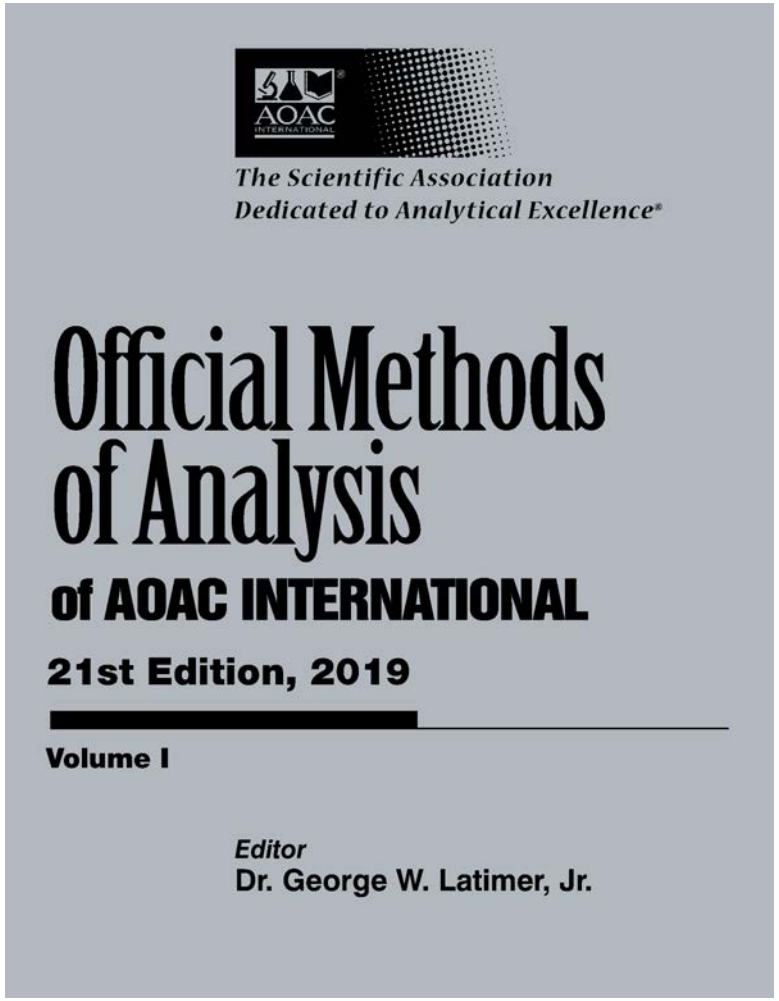
Official Methods of Analysis

- Usually submitted in response to a **Call for Methods** from one of the programs.
- Usually a *Standard Methods Performance Requirement*.
- Evaluated by an AOAC Expert Review Panel.

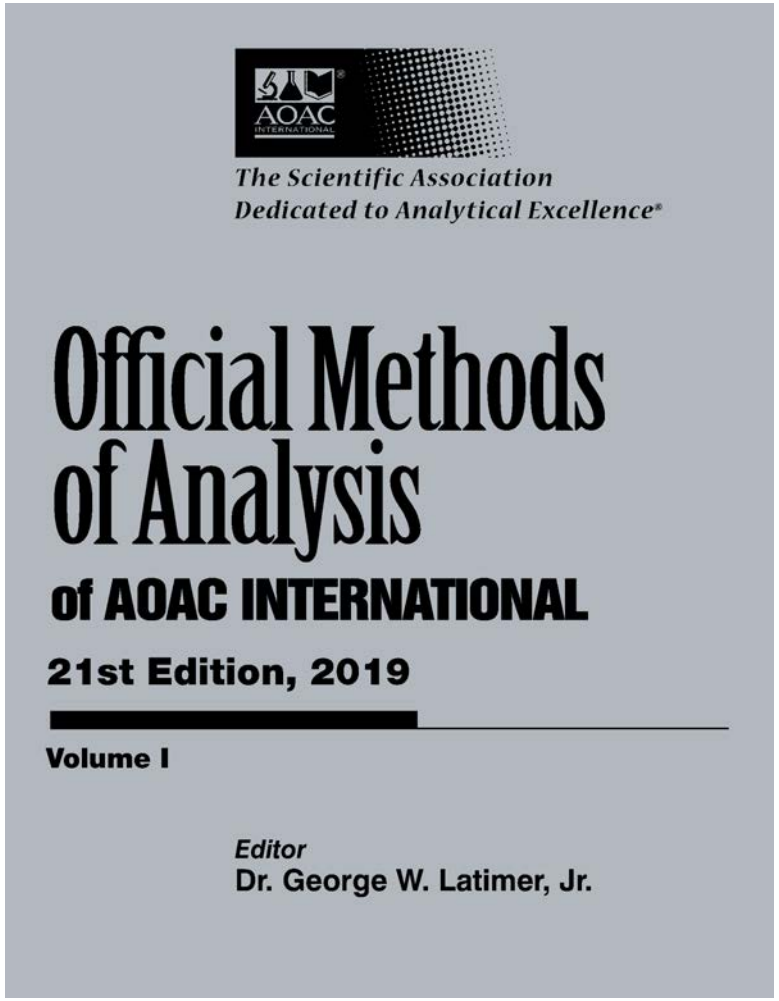


Official Methods Program

First Action *Official Methods of Analysis*

- Published in the *Official Methods of Analysis* compendium.
- Reviewed after 2 years.

Final Action *Official Methods of Analysis*



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Cannabis-Related AOAC Official Methods of Analysis

AOAC Official Method 2018.10
Cannabinoid in Dried Flowers and Oil Liquid Chromatographic Method

AOAC Official Method 2018.11
Quantitation of Cannabinoids in Cannabis Dried Plant Materials, Concentrates, and Oils using Liquid Chromatography–Diode Array Detection Technique with Optional Mass Spectrometric Detection

AOAC Official Method 2018.11

Cannabinoids are isolated from the homogenized dried plant material using two repeated extractions with ethanol (EtOH).

Oils and concentrates, such as Cannabis resins and tinctures, are dissolved using the same solvent.

The extract aliquot is filtered, diluted with methanol (MeOH), and analyzed using LC with DAD–UV.

AOAC Official Method 2018.11

Samples are quantified against standards of known concentration using a linear regression calibration function.

Identification of cannabinoids is performed based on comparison of analyte retention times and UV absorbance spectra in the sample and reference standards.

Optional high-confidence identification can be achieved by employing a mass spectrometer as a secondary detector.

AOAC Official Method 2018.11

Applicable to quantification and identification of:

cannabidiol (CBD),
cannabidiolic acid (CBDA),
cannabinol (CBN),
Delta-9-tetrahydrocannabinol (Delta-9-THC),
Tetrabydrocannabinolic acid (THCA),
cannabichromene (CBC),
cannabidivarinic acid (CBDVA),
cannabigerol (CBG),
cannabigerolic acid (CBGA),
cannabidivarin (CBDV),
delta-8-tetrahydrocannabinol (delta-8-CBD),
tetrahydrocannabivarin (THCV)

Table 3. Method performance requirements (part 1) for cannabinoids

Parameter	Requirement[a]
Limit of quantitation (LOQ), %	≤0.05
Analytical range (CBD and CBDA), %	0.05–35
Analytical range (others), %	0.05–5

[a] All calculated on dry weight basis.

Table 4. Method performance requirements (part 2) for cannabinoids

	Analytical range, %[a]		
Parameter	0.05–0.5	>0.5–5	5–35[b]
Recovery, %	85–118	90–111	95–105
RSD_r, %	≤5	≤3	≤2
RSD_R, %	≤10	≤8	≤6

[a] All calculated on dry weight basis; observed values to be compared to indicated limits for acceptability.

[b] Only applicable to CBD and CBDA.

AOAC Official Method 2018.11

Method revised in April 2020 to include a dry weight basis determination.

Revised method is now posted on the AOAC website at: http://www.eoma.aoac.org/. Search for method 2018.11.

Third Pillar: Training and Education

Training and Education

AOAC developed a one-day Method Validation Training Course in 2019.

Includes modules on:

- statistics
- chemistry methods
- microbiology methods
- AOAC procedures
- independent laboratory requirements
- interpretation and Implementation of SMPR requirements

Certificate of Attendance.

Requirement for all new independent laboratories.

NEW! STARTED IN MARCH 2020

Training and Education Working

Chairman Toby Astill

- Astill developed a 10 question survey,
- 86 respondents,
- 52 volunteers to co-lead groups,
- Volunteers represent private industry, state government, federal government, instrument manufacturers, university.

Training and Education Working

Potential areas of work:

- Experimental Error
- Chemical Measurements
- QA & Calibration Methods
- Sample Prep
- Statistics•Analytical Separations
- Mass Spec
- Micro

Potential Delivery Venue:

- Online training/webinar
- White Papers
- On-site/Laboratory site training
- Classroom

Fourth Pillar: Proficiency Testing

NEW! STARTED IN APRIL 2020

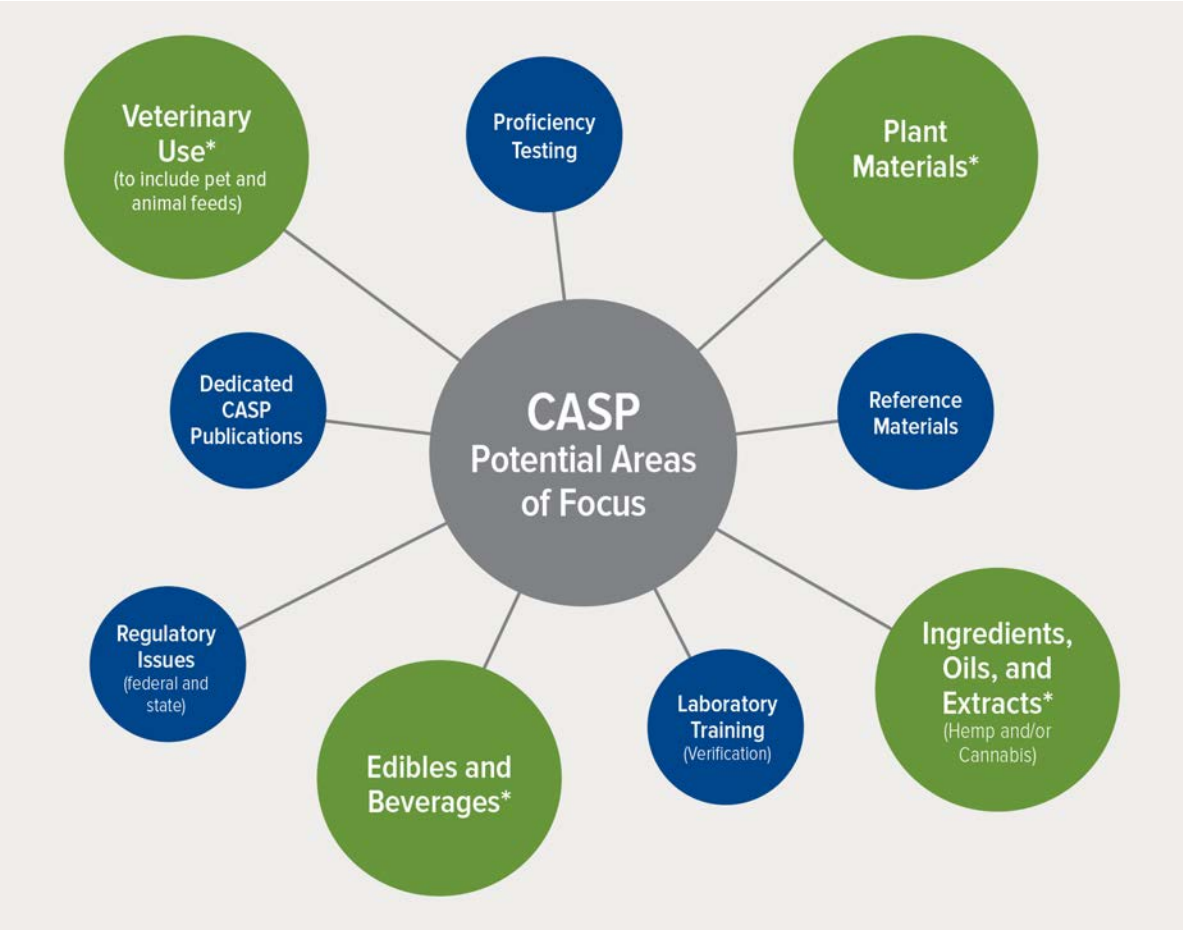
Proficiency Testing

Chairman, Dr. Brent Wilson, Research Chemist, NIST

Will build on the existing AOAC Laboratory Proficiency Program.

Potential areas of work:

- Identify currently available PT/ILC appropriate for the Hemp and/or MJ industry
- Identify industry needs
- Provide guidelines to assist laboratories in identifying appropriate PT/ILC programs



Targeting cannabis- and hemp specific standards and/or methods of analysis such as:

- potency
- pesticide residues
- biological contaminants
- chemical contaminants including select mycotoxins
- untargeted testing profiles
- method validation guidelines

Advisory Panel

Pioneer		
AFDO	SōRSE Technology	TEQ Labs
Titan Analytical	GW Pharma	PerkinElmer
Bio-Rad	Applied Food Sciences	R-Biopharm
MilliporeSigma	Ionization Labs	Supra R&D
ABC Testing	Materia Medica Laboratories	

Partner		
CV Sciences	Eurofins Scientific	

Affiliate		
Alkemist Laboratories	CEM Corporation	Crystal Diagnostics
IFT	Canopy Growth Corporation	BIOTECON Diagnostics
Hygeina	SC Labs	Medicinal Genomics
Charm Sciences		

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