Medical Marijuana Testing Advisory Council

September 26, 2019

Council's Charge

A.R.S. §36-2821(B)

The MMJ Testing Advisory Council shall make recommendations…regarding:

- Establishing a required testing program
- Testing and potency standards
- Procedural requirements for collection, storing, and testing
- Reporting results to patients and the department
- Remediation and disposal requirements

Open Meeting Law

Open Meeting Law

- Ensure completion of training and oath

What is Open Meeting Law and why do we have it?

A.R.S. § 38-431.01(A), § 38-431.09

- Protect and inform the public
- Maintain integrity of government
- Build trust between government and citizens
- Arizona's public policy requires that official deliberations and proceedings be conducted openly
- Any uncertainty should be resolved in favor of open and public meetings

What is a meeting?

A.R.S. § 38-431(4)

Means the gathering, in person or through technological devices of a quorum of the members of a public body at which the discuss, propose or take legal action, including any deliberations by a quorum with respect to that action. Includes:

- A one way electronic communication by one member of a public body that is sent to a quorum of the members of a public body that proposes legal action.
- An exchange of electronic communications among a quorum of the members of a public body that involves a discussion, deliberation or the taking of legal action by the public body concerning a matter likely to come before the public body for action.

Discuss, Propose, or Take Legal Action

- Normal use and meaning of these words will apply.
- Proposing legal action = “put forward for consideration, discussion, or adoption.”
- Includes deliberations = discussion of facts and opinions re: potential board business.
- RULE: If this occurs among a quorum of the Board IT IS A MEETING.

If it’s NOT on the agenda

- If it’s NOT on the Agenda, it CANNOT be discussed.
- All discussion must be reasonably related to an adequately described agenda item.
- If something else is brought up, add it to the agenda of a future meeting and discuss it then.

Avoiding Open Meeting Law Violations

- DO NOT discuss, propose, deliberate or take legal action on any potential Council business among a quorum of the Council outside a properly noticed public meeting.

- Council business includes anything that may foreseeably come before the Council for action.

Circumvention

- Cannot have meetings with less than a majority or use any device to circumvent the law
  - Meeting with individual members
  - Reporting what other members said
  - Polling the members

AG Opinion on Email

- No. I05-004 (R05-010)
- Re: Open Meeting Law Requirements and E-mail to and from Members of a Public Body
- Issued July 25, 2005
- Available: www.azag.gov

AG Opinion on Email

- E-mail communications among a quorum of a public body are subject to the same restrictions that apply to all other forms of communication among a quorum.

- E-mails among a quorum that involve discussions, deliberations or taking legal action on matters that may reasonably be expected to come before the board constitute a meeting through technological means.

- One-way e-mail communication by one member to quorum of members that proposes legal action is a violation even if there is no discussion, deliberation or legal action taken.

Violations and Sanctions

- Actions are null and void
  (A.R.S. § 38-431.05)

- May face civil penalties, attorney's fees or removal from office. (A.R.S. § 38-431.07)

Overview of testing-related components of statute and rule

A.R.S. §36-2803

- A.R.S. §36-2803(E) – Test
- A.R.S. §36-2803(F) – Provide results
- A.R.S. §36-2803(G) – Meet requirements
  - QA program
  - Chain of custody policies
  - Records retention
  - Valid and scientifically accurate results
  - Be accredited
  - Disposal policies

A.R.S. §36-2804.07

- Independent third party laboratories shall be certified by the department
- Certified independent third party laboratories are subject to reasonable inspection by the department

9 A.A.C. 17 Article 4

- Application for laboratory registration certificate
- Administration
- Registry identification cards
- Inventory control
- Security
- Physical plant

Tentative Meeting Plans

- 9/26/19:
  - review of testing and potency standards
- 10/24/19:
  - recommendation on testing and potency standards
  - review of sample collection & storage, reporting results, remediation, disposal
- 11/12/19
  - recommendation on sample collection & storage, reporting results, remediation, disposal
- 12/10/19
  - final recommendation report

Overview of testing & potency standards nationwide

ARIZONA DEPARTMENT
OF HEALTH SERVICES

PREPAREDNESS

ADHS' Information Gathering

- Names and locations of current labs and visited 9
- Information from labs and states on which states had best programs
- 50 states' regulations search
- Technical journal and industry article review
- Conference calls with MI and MD.
- Visited CO program

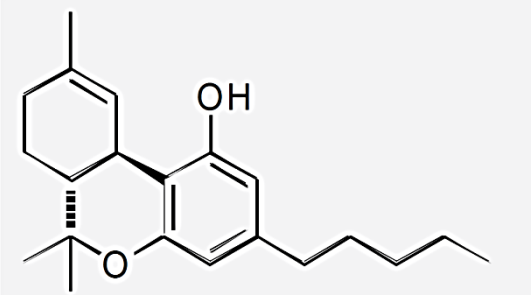
Current AZ Laboratories Testing MM

Lab Name	Address of Lab	Pest	Pot	Sol	Micro	Mtls
Lab 1	Tucson		X	X	X	
Lab 2	Mesa		X	X	X	
Lab 3	Mesa?	X				
Lab 4	Phoenix	X	X	X	X	
Lab 5	Phoenix	X	X	X	X	
Lab 6	Phoenix					X
Lab 7	Scottsdale	X	X	X	X	
Lab 8	Scottsdale		X	X	X	
Lab 9	Phoenix					X
Lab 10	Tucson	X	X	X	X	
Lab 11	Phoenix		X	X	X	

Lab 12	Chandler					
Lab 13	Phoenix					

3 Main Questions to Solve First

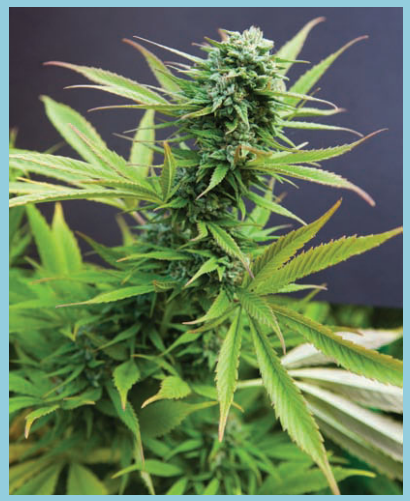
1. What parameters are we going to test for in medical marijuana?
2. What are the standards or limits of allowed contamination?
3. How is the medical marijuana being tested?



Δ^9-Tetrahydrocannabinol (Δ^9-THC)

A.R.S. § 36-2803

E. "Beginning November 1, 2020, before selling or dispensing marijuana or marijuana products to registered designated caregivers, nonprofit medical dispensaries shall test marijuana and marijuana products for medical use to determine unsafe levels of microbial contamination, heavy metals, pesticides, herbicides, fungicides, growth regulators and residual solvents and confirm the potency of the marijuana to be dispensed."



A.R.S. § 36-2803

F. … "An Independent third-party laboratory:

…

6. Must establish procedures to ensure that results are accurate, precise and scientifically valid before reporting the results."

American Herbal Pharmacopoeia®

Editors and Technical Advisors

Roy Upton RH
American Herbal Pharmacopoeia®
Scotts Valley, CA

Lyle Craker PhD
University of Massachusetts
Amherst, MA

Mahmoud ElSohly PhD
University of Mississippi
University, MS

Aviva Romm MD CPM
American Herbal Pharmacopoeia®
Lennox, MA

Ethan Russo MD
GW Pharmaceuticals
Salisbury, UK

Michelle Sexton ND BS
Americans for Safe Access
Washington, DC
The Center for the Study of Cannabis
and Social Policy
Seattle, WA

Research Associates

Jahan Marcu PhD
Green Standard Diagnostics
Henderson, NV

Diana Swisher MA
American Herbal Pharmacopoeia®
Scotts Valley, CA

Cannabis Inflorescence

Cannabis spp.

Standards of Identity, Analysis, and Quality Control

Revision 2014

AHP (2014)

Legal Notification

The following Standards of Identity, Analysis, and Quality Control of *Cannabis* are intended to provide scientifically valid methods for the analysis of cannabis and its preparations that can be used to comply with state and federal regulations and policies. The analytical methods were obtained from peer reviewed literature, have been used as part of international or federal monitoring programs for cannabis, and have been verified for their scientific validity. Methods other than those presented in this monograph may be scientifically valid and provide reliable results. However, all methods must be verified as being scientifically valid prior to use for regulatory compliance.

In the United States, cannabis is a Schedule I controlled substance under federal law; therefore, any use or possession of cannabis and its preparations is illegal except pursuant to the compassionate use Investigational New Drug exemption. These standards are not intended to support, encourage, or promote the illegal cultivation, use, trade, or commerce of cannabis. Individuals, entities, and institutions intending to possess or utilize cannabis and its preparations should consult with legal counsel prior to engaging in any such activity.

The citing of any commercial names or products does not and should not be construed as constituting an endorsement by the American Herbal Pharmacopoeia. Additionally, the reliability, and therefore ability to comply with state or federal regulations, of any conclusions drawn from the analysis of a sample is dependent upon the test sample accurately representing the entire batch. Therefore, when performing all analytical tests, a formal sampling program must be employed.

Microbial Contamination

A.R.S. § 36-2803

E. "Beginning November 1, 2020, before selling or dispensing marijuana or marijuana products to registered designated caregivers, nonprofit medical dispensaries shall test marijuana and marijuana products for medical use to determine unsafe levels of microbial contamination, heavy metals, pesticides, herbicides, fungicides, growth regulators and residual solvents and confirm the potency of the marijuana to be dispensed."

AHP Microbial Contamination

whenever applicable. Recommended tolerance limits for cannabis products are provided in Table 9 and were based on a review of national and international recommendations for botanical products as well as discussion with a variety of stakeholders (e.g., Washington State). Additional guidance for botanical products is provided in national and international compendia based on oral consumption of finished botanical products. Additionally, more restrictive limits may be adopted for medical use of cannabis, most notably when used by immune compromised individuals. Microbes such as *Aspergillus* spp., for example, can be transmitted through inhalation and are of specific concern in those with specific medical conditions (e.g. chronic granulamatous disease and cystic fibrosis) and when employing specific medical treatments (e.g., immunosuppressive therapies). Reducing total microbial risk may require specific microbial reduction treatment to the greatest level possible without compromising the putative medicinal activity. Appropriate methods for testing microbial loads can be found in the *Bacteriological Analytical Manual* (FDA 2013a).

Table 9 Microbial and fungal limits recommended for orally consumed botanical products in the US (CFU/g)

	Total viable aerobic bacteria	Total yeast and mold	Total coliforms	Bile-tolerant gram-negative bacteria	*E. coli* (pathogenic strains) and *Salmonella* spp.
Unprocessed materials*	10^5	10^4	10^3	10^3	Not detected in 1 g
Processed materials*	10^5	10^4	10^3	10^3	Not detected in 1 g
CO_2 and solvent-based extracts	10^4	10^3	10^2	10^2	Not detected in 1 g

Compendium and Comparison of State Medical Cannabis Testing

Satyam Patel, M.S., Steven Nguy, and Sherman Hom, Ph.D.

New Jersey Department of Health Public Health and Environmental Laboratories, Ewing, NJ 08628

Abstract

As of our study date, 31 states & Washington DC, had legalized medical cannabis. Of these, 26 have enacted testing regulations for a) cannabinoid content, b) herbicide and/or pesticide content, c) and/or microbiological (bacteria and/or molds) enumeration. The "and/or" statements show that great variation exists in testing regulations. Documenting safe (for consumer), legal (per state), and correctly labelled (as in FDA "Truth in Labeling" standards) medicine is the goal of testing regulations for medical cannabis. However, no compendium of state testing regulations for contaminants and cannabinoids exists. Presented here is just such a compendium-a database analyzing more than 60 sub-databases. Some of the information available: a) the states which have legalized medicinal cannabis; b) required elements for testing, by state; and c) range of maximum allowable limits, where applicable. The medical conditions for which each state has approved cannabis are also documented. Internet links for documentation are included. Compendium will be updated annually.

Some specifics: 26/31 states test CANNABINOID POTENCY (at least 4 cannabinoids: THCA, delta-9-THC, CBDA, and CBD). In every category states are identified alphabetically. 25/31 states require MICROBIAL contamination testing (primarily total aerobic bacteria, total yeast & mold, pathogenic *E coli* & *Salmonella*-as well as carcinogenic mycotoxins). All analytes are specified, e.g. aflatoxin. 20/31 states require METALS testing (14 total metals; all states: arsenic, lead, cadmium, and mercury). 26/31 states require PESTICIDES testing (total of 232 pesticides). Each state's regulated pesticides, and a database per pesticide, are documented. 23/31 states require SOLVENTS testing (84 possible solvents).

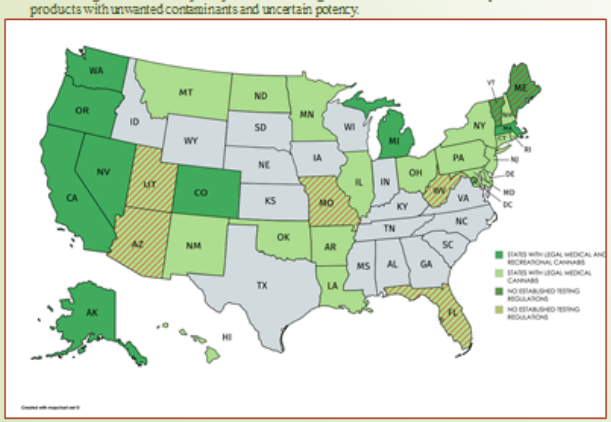
In conclusion, it is hoped that this database will be helpful for states in writing regulations, in producing safe products, accurately labelled for cannabinoid content, and free of contaminants.

Background

In the United States, the use, sale, and possession of all forms of cannabis is federally illegal[1]. Cannabis is classified as a Schedule I drug, along with heroin, LSD, and cocaine[2]. Moreover, cannabis is considered to have no accepted medical use. This regulation limits rigorous research on cannabis and a lack of scientific evidence poses risk to public health.

California became the first state to legalize cannabis for medical use in 1996 via passage of Proposition 215. Since then, 32 more states, the District of Columbia, Guam, and Puerto Rico have enacted similar laws[3].

State propositions and legislation that legalized medical cannabis protect providers and patients from being federally prosecuted[4]. These states also had to develop required testing regulations without guidance from the federal government. A major objective of these regulations is to minimize consumption of cannabis products with unwanted contaminants and uncertain potency.



NOTE: MO & UT legalized medical cannabis in November 2018 and have not promulgated testing regulations.

Methods

Links to each state's medical cannabis regulations were used to identify the location of specific information required to build this compendium

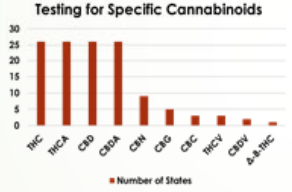
Specific information, which included products tested, analytes tested, and their maximum allowable limits, were organized for each state

Comparisons were performed to identify the analytes that were most frequently required for testing

Results

26 of the 31 states that have medical cannabis programs require testing of products.

Cannabinoid Content



[All 26 states that require testing conduct cannabinoid profile testing]

Microbial Testing

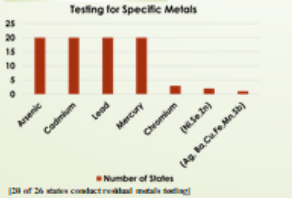
TOTAL COUNTS:	AEROBIC BACTERIA	YEAST AND MOLD	COLIFORMS
# of states testing	15	17	11
SPECIFIC TESTS:	E. COLI (PATHOGENIC)	SALMONELLA SPP.	ASPERGILLUS SPP.
# of states testing	18	21	4

[25 of 26 states conduct some microbial testing]

MYCOTOXINS:	TOTAL AFLATOXINS (B1,B2,G1,G2)	OCHRATOXIN A
# of states testing	21	20

[21 of 26 states conduct mycotoxin testing]

Residual Metals Testing



[20 of 26 states conduct residual metals testing]

Residual Pesticides Testing

Top 21 Pesticides Tested

PESTICIDE	# OF STATES TESTING	PESTICIDE	# OF STATES TESTING
Bifenthrin	13	*Paclobutrazol*	11
Imidacloprid	13	*Permethrins*	11
Myclobutanil	13	Spirotetramat	11
Abamectin	12	Trifloxystrobin	11
Bifenazate	12	Dichlorvos (DDVP)	10
Cyfluthrin	12	*Piperonyl butoxide*	10
Etoxazole	12	Acequinocyl	9
Imazalil	12	*Chlorpyrifos*	9
Pyrethrins	12	Daminozide (Alar)	9
Spinosad	12	*Malathion*	9
Spiromesifen	12	* Indicates tested positive in cannabis	

[All 26 states that require testing conduct residual pesticides testing]

Residual Solvents Testing

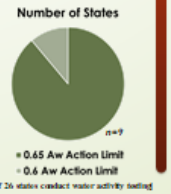
Top 12 Solvents Tested

Solvent	# of States Testing	Solvent	# of States Testing
Butane	16	Propane	12
Heptane	15	Acetone	11
Hexane	15	Pentane	11
Toluene	14	Ethanol	11
Total xylenes	14	Ethyl acetate	9
Benzene	13	Methanol	9

[23 of 26 states conduct residual solvents testing]

Water Activity Testing

Water Activity Can be used to predict and prevent microbial growth



[11 of 26 states conduct water activity testing]

Conclusions

- States that do not require testing may increase the possibility of products that may contain contaminants dangerous to human health.
- Since more than 90% of all cannabinoids are stored in trichomes in the acid form[7], required testing of cannabis products should include acid and neutral forms.
- Analyses of state testing requirements identified contaminants most frequently tested.
- Contaminant analytes' maximum allowable limits varied from state to state.
- 22 of 25 states required testing for a different combination of total microbial counts (85%).
- Since total microbial counts do not provide any information concerning pathogenicity, discussions among subject matter experts are suggested to determine the need for this testing.
- All 25 states required testing for a different combination of bacterial and fungal pathogens.
- 11 of 26 states require water activity testing (42%).
- Since high water activity may increase microbial levels in a product, states should consider adding this determination to their test menu.
- 4 metals (arsenic, cadmium, lead, and mercury) are tested by all 20 states.
- Since at least 9 pesticides were detected in cannabis products in different locations, states that do not require testing for these pesticides should consider adding them to their testing menu.
- This database and analyses may be helpful for states in enacting testing regulations to ensure the production of safe products that are accurately labelled for cannabinoid content and free of contaminants.

References

1. Controlled Substances Act, 21 U.S.C. § 841 (2018)
2. Controlled Substances Act, 21 U.S.C. § 811, 812, 871, and 956 (2018)
3. National Conference of State Legislators. (2018, November 8). *State Medical Marijuana Laws.* Retrieved from http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx
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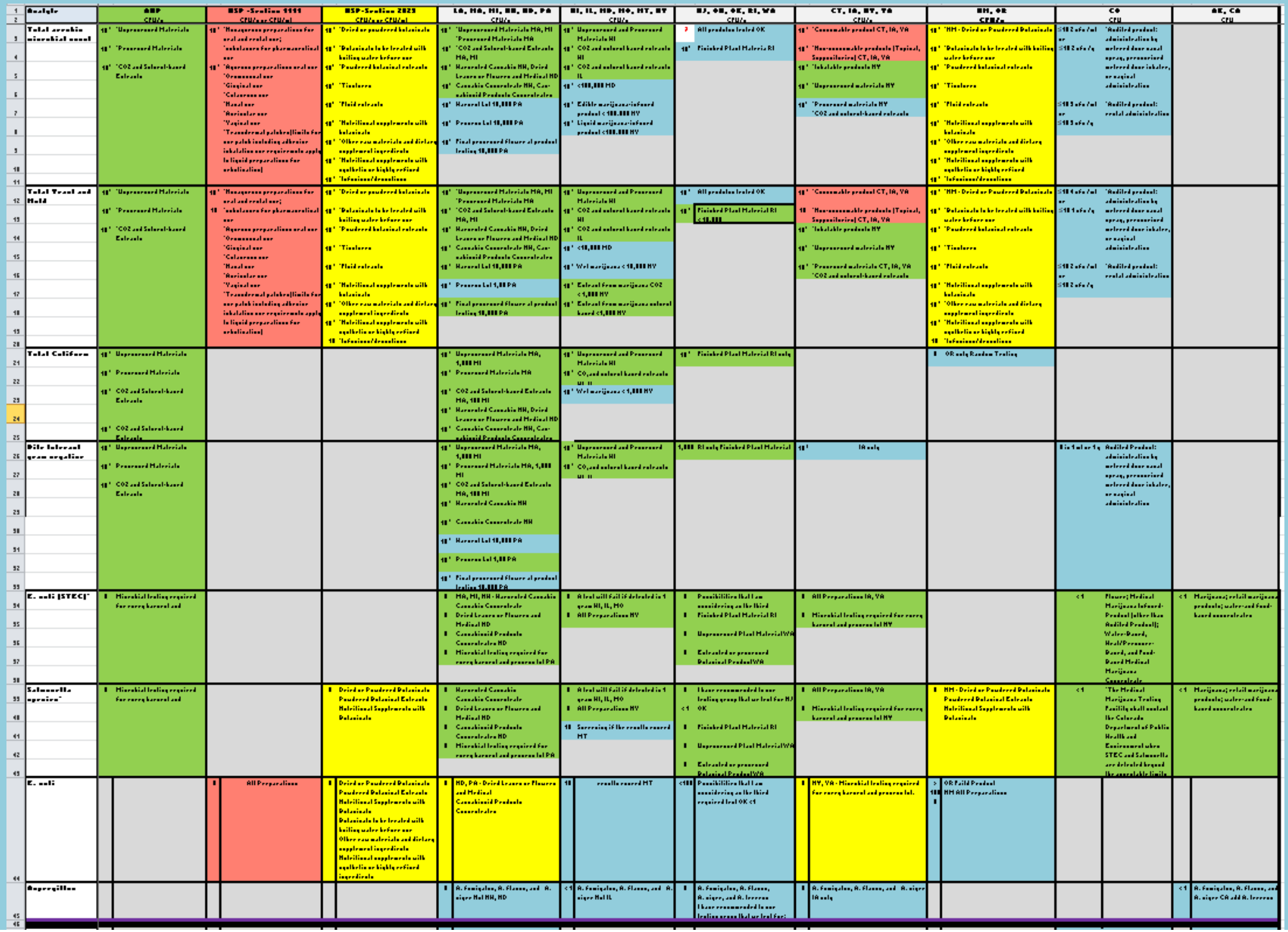
Acknowledgements

Special thanks to Mark Steen, B.S., NJ Department of Health PHEL, for assisting in the research of information, the maintenance of our compendium, and the design of this poster.

50 State Review



CANNABIS
A Clinician's Guide

State cannabis testing regulations vary widely with some states imposing no testing standards while others have adopted the United States Pharmacopeia (USP) and American Herbal Pharmacopeia (AHP) guidelines [12,13]. Some states, including New York and Hawaii, specify testing for Aspergillus, Klebsiella, Pseudomonas, Streptococcus, Mucor, and Penicillium. There is a lack of research to support the effectiveness and validity of microbial testing protocols, and no studies have been reported on beneficial endophytes on the Cannabis sativa microbiome [14].

The cannabis microbiome has been shown to have several endophytic (internal) fungi species including Penicillium citrinum, Penicilllium copticola, and several Aspergillus species [4,5]. An investigation of the fungal microbiome in several dispensary-derived cannabis products identified numerous species including some toxigenic Penicillia and Aspergilli [6]. The Penicillia species have not been reported as infectious, but several cases of serious or fatal pulmonary aspergillosis-associated cases have been reported in marijuana smoking immunocompromised patients [7].

Cannabis microbiome sequencing reveals several mycotoxic fungi native to dispensary grade *Cannabis* flowers

Quantitative PCR is agnostic to water activity and can be performed in hours instead of days. The specificity and sensitivity provides important information on samples that present risks invisible to culture based systems. The drawback to qPCR is the method's indifference to living or non-living DNA. While techniques exist to perform live-dead qPCR, the live status of the microbes is unrelated to toxin potentially produced while the microbes were alive. ELISA assays exist to screen for some toxins [51]. Current state-

Conclusions

Go to:

Several toxigenic fungi were detected in dispensary-derived *Cannabis* samples using molecular amplification and sequencing techniques. These microbes were not detected using traditional culture-based platforms. These results suggest that culture based techniques borrowed from the food industry should be re-evaluated for *Cannabis* testing to ensure that they are capable of detecting the prevalent species detected by molecular methods with adequate sensitivity. We recommend that additional sequencing studies be performed to characterize the fungal and bacterial microbiomes of a more diverse selection of *Cannabis* samples. Such sampling should include dispensary-derived samples from both indoor and outdoor crops, as well as samples from police seizures from well-provenanced foreign sources, such as Mexico. Finally, further studies should be performed to measure toxin levels in strains that test positive for toxigenic species.

TECHNICAL REPORT:
OREGON HEALTH AUTHORITY'S PROCESS TO DETERMINE WHICH TYPES OF CONTAMINANTS TO TEST FOR IN CANNABIS PRODUCTS, AND LEVELS FOR ACTION

Author
David G. Farrer, Ph.D.
Public Health Toxicologist

Oregon Health Authority
PUBLIC HEALTH DIVISION

BACKGROUND

This report describes the process the Oregon Health Authority (OHA) followed to establish the list of contaminants for cannabis testing. It also describes how OHA established an action level for each of these contaminants.

These lists and action levels have now been implemented in Oregon Administrative Rules (OAR 333-7-0010 through 333-7-0100 and OAR 333-7-0400 and 333-7-0410 Exhibit A).

This report documents the rationale and justifications for:

- The selection of target contaminants for testing; and
- Testing regimes for cannabis and cannabis-derived products.

The three major categories of contaminants targeted for testing include:

- Microbiological contaminants;
- Pesticides; and
- Solvents.

OHA is committed to evidence-based decision making when drafting and implementing OARs. As research into cannabis use and safety advances, the OARs related to cannabis testing and this report will be revised and updated to reflect the state of the science.

Not all types of cannabis products need testing for all three of these contaminant categories. Below is information on each of the three major categories of contaminants targeted for testing.

In developing the OARs and this document, OHA relied on the expertise of individuals from various organizations named in the "Acknowledgments" section. Their expertise ranged from pesticide use in Oregon, pesticide regulation in Oregon, analytical chemistry, laboratory accreditation, microbiology, cannabis processing and cannabis cultivation. They also represented a range of organizations including the Oregon Department of Agriculture, commercial analytical chemistry laboratories, state laboratories and state laboratory accreditation personnel. Throughout this document, this group will be referred to as the "Technical Expert Work Group" or the "work group."

MICROBIOLOGICAL

The Technical Expert Work Group recommended that cannabis products be tested for *E. coli* and *Salmonella.* The work group also advised that products not be allowed to go to market if any *Salmonella* is detected or if *E. coli* is detected at levels higher than 100 CFU/g. In general, bacteria cannot survive either the drying or heating processes that occur when cannabis is prepared for smoking. *Salmonella,* however, can survive when very little moisture is present, and it can easily infect humans. *E. coli* does not usually pose a significant health risk; however, its presence indicates poor sanitary conditions and that other fecal bacteria may be present. Testing for both organisms in cannabis products will, therefore, protect public health.

The only other *microbial* organisms of concern on cannabis are several species of *Aspergillus* mold. *Aspergillus* can cause respiratory infections in individuals who inhale it if they are severely immune-compromised. These individuals should avoid smoking cannabis. However, OHA Administrative Rules do not require testing for *Aspergillus;* the mold is so common in the environment that a person could pick it up many different ways. A positive test result would not mean the product is unsafe for most uses for most people. Therefore, the work group recommended that cannabis products intended for smoking and other inhalation uses include a warning about this risk for people with suppressed immune systems.

Some states have required testing of cannabis for *aflatoxins* produced by certain *Aspergillus* species. Oil-rich seeds must be present to produce these toxins on plants. Commercial cannabis does not contain these seeds. As a result, the Technical Expert Work Group recommends against such testing.

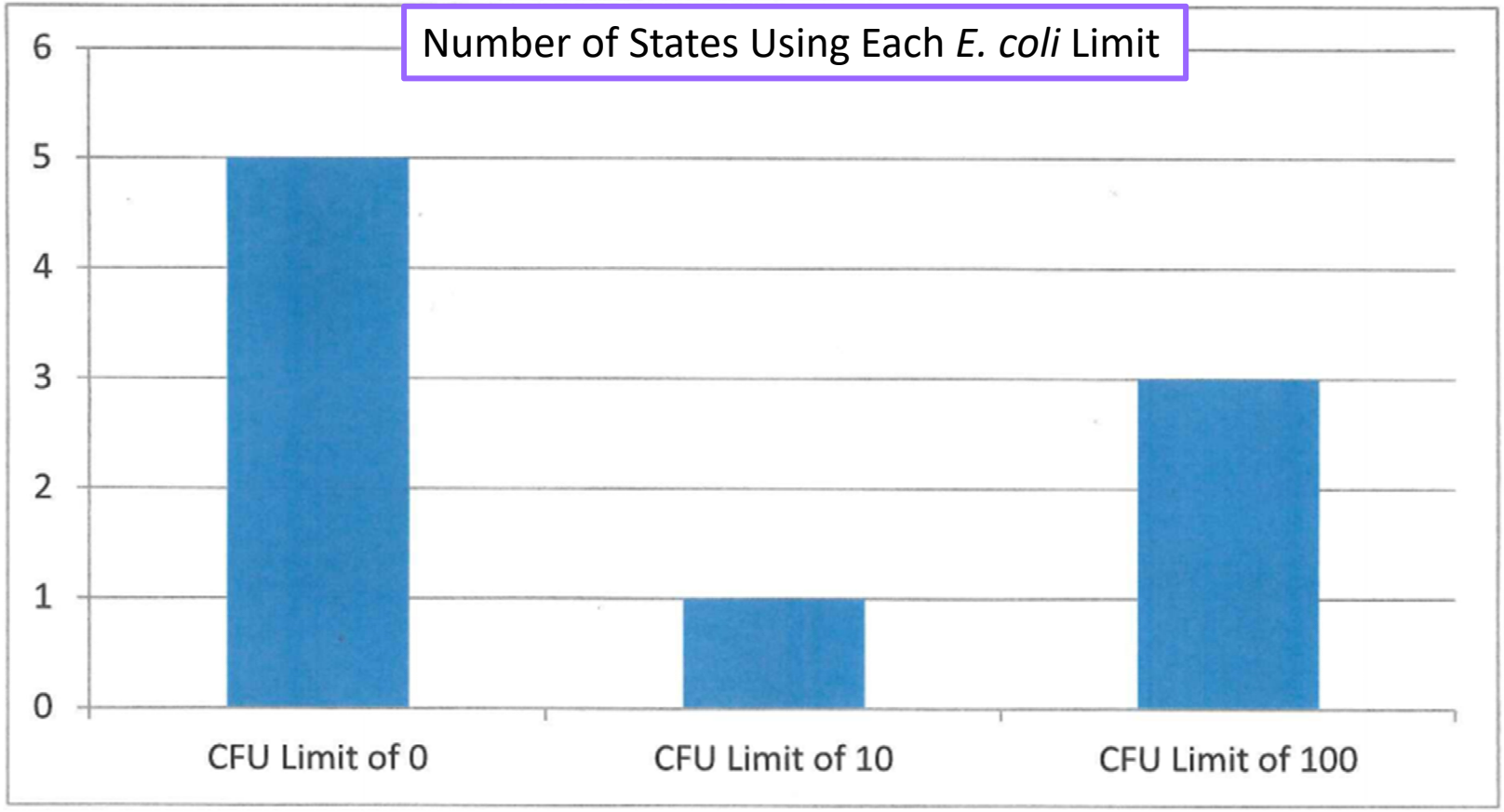
Water activity

Water activity is a measure of how moist something is in units called "A_w". Most pathogenic microbial organisms cannot grow when water activity is less than A_w 0.65. Testing for water activity and requiring water activity levels to fall below A_w 0.65 will ensure the absence of microbial growth on cannabis products during storage and before sale.

The presence of **Escherichia coli** at levels greater than 10 MPN/g in a **dairy product**, other than a **cheese** or **cheese product** made from raw **milk**, also indicates insanitary conditions.

Dairy Products - FDA

https://www.fda.gov › media › download



Microbial Contamination Standards for Consideration:

- All Medical Marijuana products tested for *E. coli* using methods from the *Bacteriological Analytical Manual (FDA 2013a).*
  - <1 CFU/g, it can be released for retail sale.
    - Unless *Aspergillus* testing required also for inhalables.
  - 1-10 CFU/g, it must be tested for the presence of *E. coli (STEC)* and *Salmonella species*. If they are detected, the product can not be released for retail sale.
  - >10 CFU/g can not be released for retail sale.
    - If a plant product tests >10 CFU/g, but is non-detect for the presence of *E. coli (STEC)* and *Salmonella species*, it can be remediated for extracted products for retail sale.

- If the test batch is found to contain levels of any microbial that could be toxic if consumed, then the department may determine that the test batch has failed contaminant testing.

<u>Microbial Contamination Considerations</u>:

-Aspergillus species? (2 options):

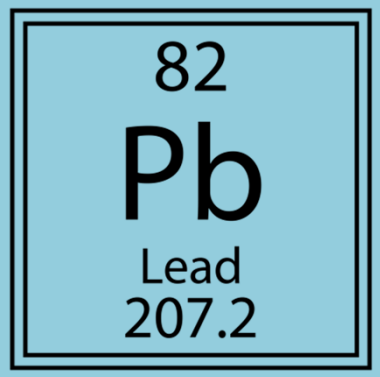
1. All medical marijuana plant inhalables shall be tested for the presence of *Aspergillus flavus*, *Aspergillus fumigatus, Aspergillus niger* and *Aspergillus terreus.* If any of these are detected in 1 gram of a product, it can not be released for retail sale.

or

2. All inhalable plant products shall be labeled to include a warning about the risk from inhaling mold for people with suppressed immune systems.

Heavy Metals

A.R.S. § 36-2803



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AHP Heavy Metals

Metal Limits

When grown in contaminated soil, cannabis accumulates heavy metals to the extent that it has been proposed as a candidate for bioremediation of toxic waste sites (Shi and Cai 2009). Siegel et al. (1988) measured 440 ng mercury per gram of cannabis in Hawaii, whose volcanic soil contains naturally high levels of mercury. Siegel notes that mercury is absorbed 10 times more efficiently by the lungs than by the gut. He calculated that smoking 100 g of volcanic cannabis per week could lead to mercury poisoning. The American Herbal Products Association (AHPA) provides manufacturers of herbal products with general recommendations for maximum heavy metals levels in herbal products, based on the daily product intake amount (Table 11). The most appropriate method for quantification of metals in medicinal products is an inductively coupled plasma-mass spectrometry (ICP-MS) method of the US Food and Drug Administration (FDA), which analyzes arsenic, cadmium,

Table 11 Metal limits recommended for herbal products in the US

Contaminating metal	Limit, µg/daily dose
Inorganic arsenic	10
Cadmium	4.1
Lead	6
Methyl mercury	2.0

Source: AHPA (2008).

Testing of Chromium?

- 2 States see a lot of chromium failures in flower, mainly from trimming.
- Harmful forms of chromium can be found in pigments, fungicides and corrosion inhibitors.

50 State Review

Metals Safety Limits by State

Analyte	USP ppm			MI, MO ppm		CA ppm		MA, RI ppm		CO ppm			AR ppm	IA, MN ppm	NY ppm	MD ppm	OK ppm	PA ppm
	Oral	Inhalable	Other	Inhalable	Other	Inhalable	Other	All Uses	Oral	Inhalable	Oral/Rectal/Vaginal	Topical						
Arsenic	1.5	0.2	1.5	0.2	1.5	0.2	1.5	0.2	1.5	0.2	1.5	3.0	0.2	1.5	0.2	0.4	0.4	0.4
Cadmium	0.5	0.2	0.2	0.2	0.5	0.2	0.5	0.2	0.5	0.2	0.5	3.0	0.2	0.3	0.2	0.4	0.44	0.3
Lead	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	10	0.5	1.0	10	0.5	1.0	0.2	1.0	1.0	1.0
Mercury	3.0	0.1	0.3	0.1	3.0	0.1	3.0	0.1	1.5	1.0	1.5	1.0	0.1	0.5	0.2	0.2	0.2	0.2
Chromium	1100	0.3	110	0.6	2.0	-	-	-	-	-	-	-	-	-	2.0	0.6	-	-
Barium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	60	-	-
Silver	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.4	-	-
Selenium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	26	-	-
Antimony	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.0	-	-	-
Copper	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.0	-	-	-
Nickel	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.0	-	-	-
Zinc	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20	-	-	-

Double USP

Analyte	AHP ug/daily dose	HI ppm	LA, VA ppm	WA ug/daily dose	MT ppm		NV ppm
					Extract	Flower	
Arsenic	10.0	10.0	10.0	10.0	10.0	2.0	2.0
Cadmium	4.1	4.0	4.1	4.1	4.1	0.82	0.82
Lead	6.0	6.0	10.0	6.0	6.0	1.2	1.2
Mercury	2.0	2.0	2.0	2.0	2.0	0.4	0.4
Chromium	-	-	-	-	-	-	-
Barium	-	-	-	-	-	-	-
Silver	-	-	-	-	-	-	-
Selenium	-	-	-	-	-	-	-
Antimony	-	-	-	-	-	-	-
Copper	-	-	-	-	-	-	-
Nickel	-	-	-	-	-	-	-
Zinc	-	-	-	-	-	-	-

5g daily dose

Analyte	CT ug/Kg BW/day	OH ug/KG	NH ppm
Arsenic	0.14	0.14	4.206
Cadmium	0.09	0.09	2.704
Lead	0.29	0.29	8.712
Mercury	0.29	0.29	8.712
Chromium	-	-	-
Barium	-	-	-
Silver	-	-	-
Selenium	-	-	-
Antimony	-	-	-
Copper	-	-	-
Nickel	-	-	-
Zinc	-	-	-

Michigan Heavy Metals Limits

Table 6. Heavy Metals Concentration Limits

Heavy metal	Action Limit for all Inhaled Marijuana (ppm)	Action Limit for other Marijuana products (ppm)
Lead	< 0.5	< 0.5
Inorganic Arsenic	< 0.2	< 1.5
Mercury	< 0.1	< 3.0
Cadmium	< 0.2	< 0.5
Total Chromium	< 0.6	2.0

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Elemental Analysis Manual

for Food and Related Products

4.7 Inductively Coupled Plasma-Mass Spectrometric Determination of Arsenic, Cadmium, Chromium, Lead, Mercury, and Other Elements in Food Using Microwave Assisted Digestion

Version 1.1 (March 2015)

Current Validation Status:

AOAC/ASTM: No

SINGLE LAB VALIDATION: YES

MULTI-LAB VALIDATION: NO

Authors:

Patrick J. Gray

William R. Mindak

John Cheng

⟨232⟩ ELEMENTAL IMPURITIES—LIMITS

INTRODUCTION

This general chapter specifies limits for the amounts of elemental impurities in drug products. Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container closure system). When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required. A risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard. Due to the ubiquitous nature of arsenic, cadmium, lead, and mercury, they (at the minimum) must be considered in the risk assessment. Regardless of the approach used, compliance with the limits specified is required for all drug products unless otherwise specified in an individual monograph or excluded in paragraph three of this introduction.

The drug products containing purified proteins and polypeptides (including proteins and polypeptides produced from recombinant or non-recombinant origins), their derivatives, and products of which they are components (e.g., conjugates) are within the scope of this chapter, as are drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides.

This chapter does not apply to radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This chapter does not apply to products based on genes (gene therapy), cells (cell therapy), and tissue (tissue engineering).

<233> ELEMENTAL IMPURITIES—PROCEDURES

INTRODUCTION

This chapter describes analytical procedures for the evaluation of elemental impurities that are suitable for the limits described in *Elemental Impurities – Limits* <232> and *Elemental Contaminants in Dietary Supplements* <2232>. Two procedures and criteria for the acceptability of alternative procedures are described. Alternative procedures that meet the validation requirements described herein are considered equivalent to Procedures 1 and 2 for the purposes of this test. In addition, system standardization and suitability evaluation using appropriate reference materials should be performed on the day of analysis. The test requirement is specified in *General Notices* or the individual monograph.

Speciation
The determination of the oxidation state, organic complex or combination is termed *speciation*. Analytical procedures for speciation are not included in this chapter but examples may be found elsewhere in the *USP-NF* and in the literature.

Definitions

Strong acid : concentrated ultra-pure nitric, sulfuric, hydrochloric, or hydrofluoric acids or Aqua Regia.

Matched matrix: Solutions having the same solvent composition as the *Sample solution*. In the case of aqueous solution, matched matrix would indicate that the same acids, acid concentrations, and mercury stabilizer are used in both preparations.

Target Elements: Elements with the potential to be present in the material under test. *Target Elements* must include lead, mercury, arsenic, and cadmium, and should include any of the remaining elemental impurities presented in General Chapter *Elemental Impurities – Limits* <232> used in the production of the material under test or the

MA Regulations

Appendix A - Table 01
Method Reference Table

Analysis	Technology	Primary Reference(s)	Ancillary Reference(s)	Comment
Residual Solvents	GC/MS	• USP <467> Residual Solvents • USP <621> Chromatography • USP <736> Mass Spectrometry	• EPA 8260C*	*Consulted for additional GC-MS and Headspace specific objectives and details on quantitation
Residual Solvents	GC/FID	• USP <467> Residual Solvents • USP <621> Chromatography • USP <736> Mass Spectrometry	• EPA 8000D* • EPA 8015D	*Consulted for additional chromatography confirmation requirements
Pesticides	LC/MS/MS	• AHP (2013) • EPA 1694*		*The AHP does not discuss methodology for the most current limits of pesticides set by MDPH. EPA 1694 was consulted for LC/MS/MS specific objectives of contaminants
Metals	ICP/MS	• USP <233> • USP <232> • USP <2232>	• EPA 6020A*	*Consulted for additional ICP-MS specific objectives
Cannabinoids	HPLC (UV-Vis or DAD)	• AHP (2013) • UNODC (2009)	• EPA 548.1*	*Consulted for additional HPLC specific objectives

Heavy Metals Considerations:

- Test for arsenic, cadmium, lead, mercury and chromium.
- Adopt USP limits for arsenic, cadmium, lead and mercury and MI limits for chromium.
- Adopt FDA and USP validated methods possibly with EPA Method support.
- If test batch is found to contain levels of any heavy metal that could be toxic if consumed, then the Department may determine that the test batch has failed contaminant testing.

Pesticides, Herbicides, Fungicides, Growth Regulators

A.R.S. § 36-2803

E. "Beginning November 1, 2020, before selling or dispensing marijuana or marijuana products to registered designated caregivers, nonprofit medical dispensaries shall test marijuana and marijuana products for medical use to determine unsafe levels of microbial contamination, heavy metals, pesticides, herbicides, fungicides, growth regulators and residual solvents and confirm the potency of the marijuana to be dispensed."

AHP Pesticides, Fungicides and Growth Regulators

Table 10 Pesticides commonly used in cannabis cultivation

Pesticide	Use	Residue Analytical Methods (RAM) Environmental Protection Agency (EPA)[1] or Literature[2]
Abamectin (Avermectins B1a and B1b)	Insecticide/acaricide	LC-FLD[1]; LC-MS/MS[2]
Acequinocyl	Insecticide/acaricide	LC/MS/MS[1]
Bifenazate	Acaricide	LC[1]; LC-MS/MS[2]
Bifenthrin (synthetic pyrethroid)	Insecticide	GC-ECD[1]; GC-MS/MS[2]
Chlormequat chloride	Plant growth regulator (PGR)	IC, LC-MS/MS[2]
Cyfluthrin (synthetic pyrethroid)	Insecticide	LC[2] (WHO 2004); GC-MS/MS[2]
Daminozide (Alar)	Plant growth regulator (PGR)	UV Spectroscopy[1]; LC-MS/MS[2]
Etoxazole	Acaricide	GC-MS(/MS)[1]
Fenoxycarb	Insecticide	LC/UV[1]; LC-MS/MS[2]
Imazalil	Fungicide	GC-ECD[1]; LC-MS/MS[2]
Imidacloprid	Insecticide	LC-MS/MS[2]
Myclobutanil	Fungicide	GC-ECD; GC-NPD[1]; GC-MS/MS)[2]; LC-MS/MS[2]
Paclobutrazol	Plant growth regulator (PGR); fungicide	LC-MS/MS[2]
Pyrethrins*	Insecticide	GC-ECD[1]
Spinosad	Insecticide	LC-MS/MS; immunoassay[1]
Spiromesifen	Insecticide	GC-MS[1]; LC-MS/MS[2]
Spirotetramat	Insecticide	LC/LC-MS/MS[2]
Trifloxystrobin	Fungicide	GC-NPD[1]; GC-MS/MS[2]; LC-MS/MS[2]

ECD = Electron capture detector; FLD = Fluorescence detector; GC = Gas chromatography; LC = Liquid chromatography; IR = Infrared spectroscopy; MS = Mass spectrometry; NMR = Nuclear magnetic resonance; NPD = Nitrogen phosphorous detector.

No herbicides In AHP.

List of Herbicides Approved for Use in Vegetables **UofA 2011**

Herbicide	Vegetable crop(s)	Date First Registered	Date New Registrations
EPTC (Eptam)	Carrots	1960	2009
Linuron (Lorox)	Spinach	1962	In progress
Triallate (Fargo)	Spinach	1962	in progress
DCPA (Dacthal)	Cole crops, Onions, Lettuce (Formulation and new uses)	1965	2002 and in progress
Bentazon (Basagran)	Onions, carrots	1968	In progress
Pronamide (Kerb)	Lettuce (Formulation change & Chemigation)	1969	2004 and 2011
Napropamide (Devrinol)	Lettuce	1969	In progress
Pendimethalin (Prowl H2O)	Cole crops, onions, transplanted lettuce (and Formulation change)	1975	2008 and In progress
Oxyfluorfen (GoalTender)	Cole crops, onions, celery, leeks (Formulation change and chemigation)	1976	2005 and in progress
Metolachlor (Dual Magnum)	Spinach, carrots, transplanted lettuce, peppers	1977	In progress
Clopyralid (Stinger)	Cole crops	1987	2003
Dimethenamid (Outlook)	Carrots, onions, sweet corn	1993	In progress
Halosulfuron (Sandea)	Melons	1993	2004
Carfentrazon (Aim)	Melons, transplanted fruity vegetables	2000	In progress
Flumioxazin (Chateau)	Onions, asparagus	2001	In progress
Imazamox (Raptor)	Lettuce	2001	In progress

ADOT Vegetation Management Guidelines - Herbicides

Attachment 1: Herbicide List

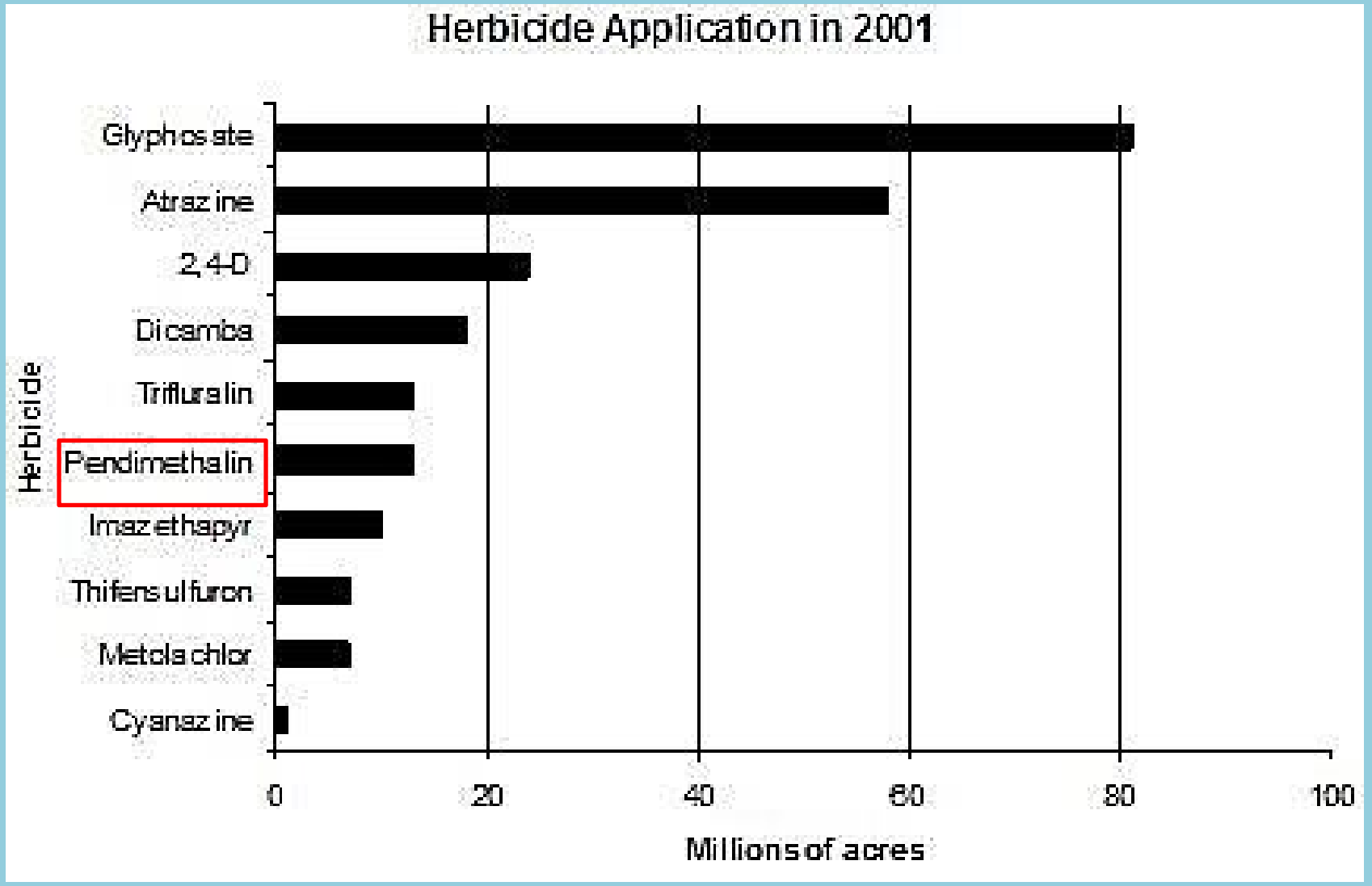
Active Ingredient	BLM[1]	USFS[2]	Selective?	Controls	Pre-Emergent	Post-Emergent	Stream Concern	Mode of Action	Trade Names
2,4-D	Y	Y	Selective	broadleaf		y	n	hormone mimic	Clean Amine
Aminocyclo-pyrachlor			Selective	broadleaf, grasses		y	y	growth regulator	Perspective, Streamline
Aminopyralid		Y	Selective	broadleaf		y	n	growth regulator	Milestone
Bromacil	Y		Non-Selective	broadleaf, grasses	y	y		photosynthesis inhibitor	Hyvar X
Chlorsulfuron	Y	Y	Selective	broadleaf	y	early	y	mitosis inhibitor	Telar
Clopyralid	Y	Y	Selective	broadleaf		Y	y	growth regulator	Stinger, Transline
Dicamba	Y	Y	Selective	broadleaf		y	y	growth regulator/ hormone mimic	Vanquish, Weedmaster
Diflufenzopyr	Y		Non-Selective	broadleaf		y		auxin transport inhibitor	Overdrive
Diquat	Y		Non-Selective	aquatic broadleaf		y	n	photosynthesis inhibitor	Spectracide
Diuron	Y		Non-Selective	broadleaf	y	y	y	photosynthesis inhibitor	Karmex, Diuron
Fluridone	Y		Non-Selective	submerged aquatic broadleaf		y	n	carotenoid synthesis inhibitor	Sonar, Avast
Fluroxypyr		Y	Selective	broadleaf		y	n	hormone mimic	Vista
Glyphosate	Y	Y	Non-selective	all		y	n	protein inhibitor	Roundup, Honcho, Rodeo
Hexazinone	Y		Non-selective	woody		y		photosynthesis inhibitor	Velpar
Imazapic	Y	Y	Rate Selective	all	m	y		amino acid inhibitor	Plateau
Imazapyr	Y	Y	Non-selective	all	y	y	n	protein inhibitor	Habitat, Arsenal
Indaziflam			Selective	broadleaf, grasses	y	y	y	cellulose biosynthesis inhibitor	Esplanade
Isoxaben		Y	Selective	broadleaf	y		n	disrupts root development	Gallery
Metsulfuron-methyl	Y	Y	Selective	broadleaf		y		protein inhibitor	Escort, Ally
Pendimethalin		Y	Non-selective	broadleaf, grasses	y		n	mitosis inhibitor	Pendulum
Picloram	Y	Y	Rate Selective	broadleaf		y	y	growth regulator	Tordon
Prodiamine			Selective	broadleaf, grasses	y			seedling growth inhibitor	Evade
Sethoxydim		Y	Selective	grasses		y	n	amino acid inhibitor	Poast
Sulfometuron-methyl	Y	Y	Non-selective	broadleaf, grasses	y	y	y	amino acid inhibitor	Oust
Tebuthiuron	Y	Y	Selective	woody vegetation	y	y	y	photosynthesis inhibitor	Spike
Triclopyr	Y	Y	Selective	woody, perennial broadleaf		y	n	growth regulator	Garlon, Remedy, Redeem

Notes

[1] Approved in the BLM-ADOT Herbicide Environmental Assessment (2015)

[2] Approved in the USFS Region 3-ADOT Vegetation Management Environmental Assessment (2003); not all National Forests have approved this full list of herbicides in their separate Forest herbicide NEPA documents

USEPA


Herbicide Application in 2001
Glyphosate
Atrazine
2,4-D
Dicamba
Trifluralin
Pendimethalin
Imazethapyr
Thifensulfuron
Metolachlor
Cyanazine
Herbicide
0
20
40
60
80
100
Millions of acres

2015

TECHNICAL REPORT:
OREGON HEALTH AUTHORITY'S PROCESS TO DETERMINE WHICH TYPES OF CONTAMINANTS TO TEST FOR IN CANNABIS PRODUCTS, AND LEVELS FOR ACTION

Author
David G. Farrer, Ph.D.
Public Health Toxicologist

Oregon Health Authority
PUBLIC HEALTH DIVISION

PESTICIDES

Target analyte list development

Work group members established three lists of *target analytes* related to pesticides. OHA compiled the three lists and filtered it by criteria agreed upon by the work group.

- Work group members created the first list as described in Appendix 1 of a white paper titled "Pesticide Use on Cannabis" published by the Cannabis Safety Institute in June 2015.(1) This list contained 123 active ingredients.
- The work group generated the second list by identifying compounds that overlapped between various other lists. This included the first list described above; Oregon, Nevada or Colorado regulations for medical or recreational marijuana; and other lists.
- The work group generated the third list based on integrated pest management guidance for several crops grown in the Pacific Northwest. It also included a search of the Pesticide Information Center Online (PICOL) database. Additionally, work group members made a list of the active ingredients in pesticide products available at a local hardware store. Once this information was compiled, work group members compared their master list to the first two lists described above and removed any redundancies.

OHA compiled these three submitted lists and removed duplicates. This resulted in a starting list of 188 pesticide analytes.

Table 1 describes the process by which the work group scored and filtered the compiled list of 188 pesticide analytes. First, they scored active ingredients based on general (human) toxicity, analytical capacity, detection frequency in cannabis samples in Oregon and general availability. All scoring parameters were reduced to a four-point scale (from zero to three). Then, OHA added scores across the parameters to get a composite score for each pesticide active ingredient.

An OHA toxicologist initially scored active ingredients for toxicity. An Oregon State University toxicologist and an Oregon Department of Agriculture (ODA) representative with some training in toxicology reviewed and approved the toxicity scoring. Three analytical laboratories participating in the work group independently scored analytical capacity and detection frequency in Oregon's cannabis.

OHA averaged these independently submitted scores and rounded averaged analytical capacity and detection frequency scores to the nearest whole number (0.5 was rounded to 1).

ODA scored general availability based on registration status and general knowledge of use patterns. Every pesticide product must be registered for specific uses with ODA. As a result, ODA has expert knowledge on which pesticides are used for which purposes in Oregon.

Table 1. Scoring process for each target pesticide analyte on OHA's compiled list

	Low (0) — Priority to keep on list — High (3)			
	0	**1**	**2**	**3**
General toxicity	No data	*Fungicides*, plant growth regulators	Pyrethroid, neonicotinoid, pyrazole and pyrimidine, and macrocyclic lactone insecticides and *acaricides* and insect growth regulators	*Organophosphate*, organochlorinated and *carbamate* insecticides.
Analytical capability	Not tested	Expensive and/ or analytically challenging to test in cannabis	Some labs said feasible, other labs said not feasible	Multi-instrument, "easy" clean-up, all labs in agreement
Detection frequency (in cannabis)	Tested but never detected	Not tested	Single detection	Multiple detections
Availability	Not available or ODA experience suggested this analyte would not be used or detected in cannabis	Restricted use pesticide registered for a single crop or use	Restricted use pesticide registered for multiple crops or uses	General use pesticide (no license or other certification needed to purchase or use products with this active ingredient); ODA knowledge that the analyte is frequently used illegally and likely to be used on cannabis

Once scoring was complete, OHA applied an extra point to the composite score for each analyte that scored 2 or higher for detection frequency in cannabis. Detection frequency indicates this pesticide active ingredient is already being used in Oregon's cannabis. As a result, OHA placed greater emphasis on detection frequency than on other parameters in cannabis. This weighting process ensured that composite scores would reflect this emphasis on pesticides known to be used in Oregon's cannabis.

Every analyte with a composite score of 8.5 or higher was retained on the final list. Analytes with composite scores below 8.5 were removed from the list. OHA selected 8.5 as the cutoff score because it was the highest score that captured all pesticide active ingredients that had ever been detected in cannabis in Oregon.

Pesticides, continued

Table 2. Pesticide analytes and their action levels

Analyte	Chemical Abstract Services (CAS) Registry number	Action level ppm
Abamectin	71751-41-2	0.5
Acephate	30560-19-1	0.4
Acequinocyl	57960-19-7	2
Acetamiprid	135410-20-7	0.2
Aldicarb	116-06-3	0.4
Azoxystrobin	131860-33-8	0.2
Bifenazate	149877-41-8	0.2
Bifenthrin	82657-04-3	0.2
Boscalid	188425-85-6	0.4
Carbaryl	63-25-2	0.2
Carbofuran	1563-66-2	0.2
Chlorantraniliprole	500008-45-7	0.2
Chlorfenapyr	122453-73-0	1
Chlorpyrifos	2921-88-2	0.2
Clofentezine	74115-24-5	0.2
Cyfluthrin	68359-37-5	1
Cypermethrin	52315-07-8	1
Daminozide	1596-84-5	1
DDVP (Dichlorvos)	62-73-7	0.1
Diazinon	333-41-5	0.2
Dimethoate	60-51-5	0.2
Ethoprophos	13194-48-4	0.2
Etofenprox	80844-07-1	0.4
Etoxazole	153233-91-1	0.2
Fenoxycarb	72490-01-8	0.2
Fenpyroximate	134098-61-6	0.4
Fipronil	120068-37-3	0.4
Flonicamid	158062-67-0	1
Fludioxonil	131341-86-1	0.4
Hexythiazox	78587-05-0	1

Analyte	Chemical Abstract Services (CAS) Registry number	Action level ppm
Imazalil	35554-44-0	0.2
Imidacloprid	138261-41-3	0.4
Kresoxim-methyl	143390-89-0	0.4
Malathion	121-75-5	0.2
Metalaxyl	57837-19-1	0.2
Methiocarb	2032-65-7	0.2
Methomyl	16752-77-5	0.4
Methyl parathion	298-00-0	0.2
MGK-264	113-48-4	0.2
Myclobutanil	88671-89-0	0.2
Naled	300-76-5	0.5
Oxamyl	23135-22-0	1
Paclobutrazol	76738-62-0	0.4
Permethrins*	52645-53-1	0.2
Phosmet	732-11-6	0.2
Piperonyl_butoxide	51-03-6	2
Prallethrin	23031-36-9	0.2
Propiconazole	60207-90-1	0.4
Propoxur	114-26-1	0.2
Pyrethrins†	8003-34-7	1
Pyridaben	96489-71-3	0.2
Spinosad	168316-95-8	0.2
Spiromesifen	283594-90-1	0.2
Spirotetramat	203313-25-1	0.2
Spiroxamine	118134-30-8	0.4
Tebuconazole	80443-41-0	0.4
Thiacloprid	111988-49-9	0.2
Thiamethoxam	153719-23-4	0.2
Trifloxystrobin	141517-21-7	0.2

* Permethrins should be measured as cumulative residue of cis- and trans-permethrin isomers (CAS numbers 54774-45-7 and 51877-74-8).

† Pyrethrins should be measured as the cumulative residues of pyrethrin 1, cinerin 1 and jasmolin 1 (CAS numbers 121-21-1, 25402-06-6, and 4466-14-2 respectively).

Compiled State Pesticide, Fungicide, Growth Regulator, Herbicide Lists and Standards

Pesticides/PGR Safety Limits by State

Analyte	USP ppm	AOAC ppm Plant Materia	MN ppm	R, A ppm	MI ppm	MO ppm	MD ppm	IA ppm	MT ppm Flower	MT ppm Extract	FL, H ppm	PA ppm	CA ppm All	CA ppm Inhalable	CA ppm Other	NH ppm	RI ppm	MA ppm	CT ppm	CO ppm Flowe	NY ppm
Abamectin (Avermectins)		0.05		0.5	0.5	0.5	0.5		0.5	2.5	1.0	0.1		0.1	0.3	0.01	0.01		0.01	0.07	
Acephate	0.1	0.1	0.1	0.4	0.4	0.4					1.0	0.1		0.1	5.0	0.01					
Acequinocyl		0.1		2.0	2.0	2.0			2.0	10	1.0	0.1		0.1	4.0	0.01	0.01		0.02		Required
Acetamiprid		0.1		0.2	0.2	0.2	0.2	0.2			1.0	0.1		0.1	5.0	0.01					
Aldicarb		0.1		0.4	0.4	0.4	0.4	0.4			1.0	0.1	0.1			0.01					
Azoxystrobin		0.02		0.2	0.2	0.2	0.2	0.2			1.0	0.1		0.1	40	0.01				0.02	
Bifenazate		0.01		0.2	0.2	0.2	0.2	0.2	0.2	1.0	1.0	0.1		0.1	5.0	0.01	0.01	0.01	0.1	0.02	Required
Bifenthrin		0.01		0.2	0.2	0.2	0.2		0.2	1.0	1.0	0.1		3.0	0.5	0.01	0.01	0.01	0.05		
Boscalid		0.1		0.4	0.4	0.4	0.4	0.4			1.0	0.1		0.1	10	0.01					
Carbaryl		0.2		0.2	0.2	0.2	0.2	0.5			1.0	0.1	0.5			0.01					
Carbofuran		0.1		0.2	0.2	0.2	0.2	0.2			1.0	0.1	0.1			0.01					
Chlorantraniliprole		0.2		0.2	0.2	0.2	0.2	0.2			1.0	0.1		10	40	0.01					
Chlorfenapyr		0.1		1.0	1.0	1.0					1.0	0.1	0.1			0.01					
Chlorpyrifos (-ethyl)	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.6			1.0	0.1	0.1			0.01					
Clofentezine		0.1		0.2	0.2	0.2	0.2				1.0	0.1		0.1	0.5	0.01					
Cyfluthrin	0.1	0.01	0.1	1.0	1.0	1.0	1.0		1.0	5.0	1.0	0.1		2.0	1.0	0.01	0.01	0.01	0.02		Required
Cypermethrin	1.0	0.05	1.0	1.0	1.0	1.0		18			1.0	0.1		1.0	1.0	0.01					
Daminozide		0.05		1.0	1.0	1.0	1.0		1.0	5.0		0.1	0.1			0.01	0.01				
Diazinon	0.5	0.1	0.5	0.2	0.2	0.2		2.6			1.0	0.1		0.1	0.2	0.01					
Dichlorvos (DDVP)	1.0	0.1	1.0	0.1	1.0	1.0		0.1			1.0	0.1	0.1			0.01					
Dimethoate	0.1	0.1	0.1	0.2	0.2	0.2	0.2				1.0	0.1	0.1			0.01					
Ethoprophos		0.1		0.2	0.2	0.2		0.4			1.0	0.1	0.1			0.01					
Etofenprox		0.1		0.4	0.4	0.4		0.4			1.0	0.1	0.1			0.01					
Etoxazole		0.01		0.2	0.2	0.2	0.2		0.2	1.0	1.0	0.1		0.1	1.5	0.01	0.01	0.01	0.01	0.01	Required
Fenoxycarb		0.1		0.2	0.2	0.2			0.2	1.0		0.1	0.1			0.01	0.01				
Fenpyroximate		0.1		0.4	0.4	0.4	0.5				1.0	0.1		0.1	2.0	0.01					
Fipronil		0.1		0.4	0.4	0.4	0.4	1.0			1.0	0.1	0.1			0.01					
Flonicamid		0.1		1.0	1.0	1.0	1.0	1.0			1.0	0.1		0.1	2.0	0.01					Required
Fludioxonil		0.02		0.4	0.4	0.4	0.4				1.0	0.1		0.1	30	0.01					Required
Hexythiazox		0.1		1.0	1.0	1.0	1.0				1.0	0.1		0.1	2.0	0.01					
Imazalil		0.01		0.2	0.2	0.2	0.2		0.2	1.0	1.0	0.1	0.1			0.01	0.01	0.01	0.1	0.04	
Imidacloprid		0.01		0.4	0.4	0.4	0.4	0.4	0.4	2.0	1.0	0.1		5.0	3.0	0.01	0.01	0.01	0.05	0.02	Required
Kresoxim-methyl		0.1		0.4	0.4	0.4	0.4				1.0	0.1		0.1	1.0	0.01					
Malathion	1.0	0.05	1.0	0.2	0.2	0.2	0.2				1.0	0.1		0.5	5.0	0.01				0.05	
Metalaxyl		0.2		0.2	0.2	0.2	0.2	0.2			1.0	0.1		2.0	15	0.01					
Methiocarb		0.1		0.2	0.2	0.2	0.2	0.4			1.0	0.1	0.1			0.01					
Methomyl		0.4		0.4	0.4	0.4	0.4	0.4			1.0	0.1		1.0	0.1	0.01					
Methyl parathion		0.1		0.2	0.2	0.2		8.5				0.1	0.1			0.01					
MGK-264		0.2		0.2	0.2	0.2					1.0	0.1				0.01					
Myclobutanil		0.01		0.2	0.2	0.2	0.2	0.3	0.2	0.6	1.0	0.1		0.1	9.0	0.01	0.01	0.01	0.02	0.04	Required
Naled		0.1		0.5	0.5	0.5	0.5				1.0	0.1		0.1	0.5	0.01					
Oxamyl		0.5		1.0	1.0	1.0	1.0	1.0			1.0	0.1		0.5	0.2	0.01					
Paclobutrazol		0.05		0.4	0.4	0.4	0.4		0.4	2.0	1.0	0.1	0.1			0.01	0.01		0.4		
Permethrin	1.0	0.04	1.0	0.2	0.2	0.2	0.5	1.1			1.0	0.1		0.5	20	0.01				0.04	
Phosmet	0.05	0.02	0.05	0.2	0.2	0.2	0.2				1.0	0.1		0.1	0.2	0.01					
Piperonyl butoxide	3.0	0.5	3.0	2.0	2.0	2.0	1.0				1.0	0.1		3.0	8.0	0.01					Required
Prallethrin		0.05		0.2	0.2	0.2					1.0	0.1		0.1	0.4	0.01					
Propiconazole		0.05		0.4	0.4	0.4	0.4				1.0	0.1		0.1	20	0.01					
Propoxur		0.05		0.2	0.2	0.2					1.0	0.1	0.1			0.01					
Pyrethrins		0.5		1.0	1.0	1.0	1.0		1.0	5.0	1.0			0.5	1.0	0.01			0.05		Required
Pyridaben		0.1		0.2	0.2	0.2		0.2			1.0	0.1		0.1	3.0	0.01					
Spinosad		0.06		0.2	0.2	0.2	0.2		0.2	1.0	1.0	0.1		0.1	3.0	0.01	0.01		0.01	0.06	Required
Spiromesifen		0.01		0.2	0.2	0.2	0.2		0.2	1.0		0.1		0.1	12	0.01	0.01	0.01	0.02	0.03	
Spirotetramat		0.02		0.2	0.2		0.2		0.2	1.0	1.0	0.1		0.1	13	0.01	0.01		0.2	0.02	Required
Spiroxamine		0.1		0.4	0.4	0.4		2.0				0.1	0.1			0.01					
Tebuconazole		0.01		0.4	0.4	0.4		0.4			1.0	0.1		0.1	2.0	0.01				0.01	
Thiacloprid		0.1		0.2	0.2	0.2	0.2	0.2			1.0	0.1	0.1			0.01					
Thiamethoxam		0.05		0.2	0.2	0.2	0.2	0.2			1.0	0.1		5.0	4.5	0.01					Required
Trifloxystrobin		0.01		0.2	0.2	0.2	0.2		0.2	1.0	1.0	0.1		0.1	30	0.01	0.01	0.01	0.05		Required
Captan		0.05										0.1		0.7	5.0						
Chlordane	0.05	0.1	0.05										0.1								
Chlormequat Chloride		0				0.2			1.0	5.0						0.01	0.01				

LABORATORY INFORMATION BULLETIN

Collaboration of the QuEChERS Procedure for the Multiresidue Determination of Pesticides by LC-MS/MS In Raw Agricultural Commodities

Chris Sack*, Michael Smoker, KAN, *Lenexa, KS*
Narong Chamkasem, *SRL, Atlanta, GA*
Richard Thompson, Greg Satterfield, *ARL, Jefferson, AR*
Shaun MacMahon, Claude Masse, Michael, *NERL, Jamaica, NY*
Greg Mercer, Barbara Neuhaus, *PRL-NW, Bothell, WA*
Irene Cassias, Eugene Chang *PRL-SW, Irvine, CA*
Jon Wong, Kai Zhang, *CFSAN, College Park, MD*
*Author to whom correspondence should be addressed chris.sack@fda.ora.gov

Six FDA pesticide laboratories participated in a collaborative study to evaluate the QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) multiresidue method with LC-MS/MS determination for pesticides the raw agricultural commodities orange, carrot and spinach. Each matrix was fortified at 0, 20, 100, 400, and 1000 ppb, levels and analyzed using a single level (200 ng/mL, equivalent to 400 ppb fortification level) calibration standard in solvent. From the data specificity, accuracy, reproducibility, method uncertainty (MU), method detection limit (MDL), linearity, and the extended range of the method were evaluated. 169 of 174 analytes reported met minimum validation performance specifications. No false positive responses were detected in controls of the three matrices. 169 had recoveries between 50-150 % and 165 had recoveries between 70-130 %. The RSDs of recoveries for 170 compounds was ≤ 15 %, and 167 were ≤ 10 %. The MUs of only two compounds exceeded 30 %. 161 compounds had MDL ≤ 10 ppb, and the MDLs of only two exceeded 20 ppb. Recoveries of 170 compounds for the 100 ppb spikes (equivalent to 25 % of the calibration level) were within 50-150 %, and 166 were between 70-130 %. Recoveries of 169 compounds for the 1000 ppb spikes (equivalent to 250 % of the calibration level) were within 50-150 %. A matrix effect study indicated all three matrices caused a small net suppressing effect, the most pronounced attributable to the citrus matrix.

INTRODUCTION

In 2003, Anastassiades et al. introduced a new approach to the extraction of pesticides from fresh fruits and vegetables with acetonitrile, called QuEChERS (*Quick, Easy, Cheap, Effective, Rugged and Safe).*[1] Since then numerous modifications and studies of the procedure have been published.[2-16] In all the studies cited

J Food Sci Technol. 2015 Jul; 52(7): 4001–4014.
Published online 2014 Jul 14. doi: 10.1007/s13197-014-1473-9
PMCID: PMC4486543
PMID: 26139867

Simultaneous analysis of herbicides pendimethalin, oxyfluorfen, imazethapyr and quizalofop-*p*-ethyl by LC–MS/MS and safety evaluation of their harvest time residues in peanut (*Arachis hypogaea* L.)

Ajoy Saha,✉ Ahammed Shabeer T. P., Kaushik Banerjee, Sandip Hingmire, Debarati Bhaduri, N. K. Jain, and Sagar Utture

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Abstract

Go to:

This paper reports a simple and rapid method for simultaneous determination of the residues of selected herbicides viz. pendimethalin, oxyfluorfen, imazethapyr and quizalofop-*p*-ethyl in peanut by liquid chromatography-tandem mass spectrometry (LC-MS/MS). A modified approach of the QuEChERS methodology was used to extract the herbicides from the peanut kernel without any clean-up. The method showed excellent linearity ($r^2 > 0.99$) with no significant matrix effect. Accuracy of the method in terms of average recoveries of all the four herbicides ranged between 69.4 –94.4 % at spiking levels of 0.05, 0.10 and 0.25 mg kg^{-1} with intra-day and inter-day precision RSD (%) between 2.6–16.6 and 8.0–11.3, respectively. Limit of quantification (LOQs) was 5.0 µg kg^{-1} for pendimethalin, imazethapyr and quizalofop-*p*-ethyl and 10.0 µg kg^{-1} for oxyfluorfen. The expanded uncertainties were <11 % for determination of these herbicides in peanut. The proposed method was successfully applied for analysis of these herbicide residues in peanut samples harvested from the experimental field and the residues were below the detection level.

J Food Sci Tech

LC-MS/MS And GC/MS

10.1.04

AOAC Official Method 2007.01 Pesticide Residues in Foods by Acetonitrile Extraction and Partitioning with Magnesium Sulfate

Gas Chromatography/Mass Spectrometry and Liquid Chromatography/Tandem Mass Spectrometry

First Action 2007

[Applicable for the following pesticides in grapes, lettuces, and oranges: atrazine, azoxystrobin, bifenthrin, carbaryl, chlorothalonil, chlorpyrifos, chlorpyrifos-methyl, λ-cyhalothrin (incurred in lettuces), cyprodinil, *o,p'*-DDD, dichlorvos, endosulfan sulfate, ethion (incurred in oranges), imazalil, imidacloprid, kresoxim-methyl (incurred in grapes), linuron, methamidophos, methomyl, permethrins (incurred in lettuces) procymidone, pymetrozine, tebuconazole, thiabendazole (incurred in oranges), tolylfluanid (degraded in lettuces), and trifluralin. These were representative pesticide analytes chosen in representative matrixes, and the method is expected to be applicable to many other similar pesticides and matrixes. Limits of quantitation were demonstrated to be <10 ng/g.]

See Tables **2007.01A–E** for the results of the interlaboratory study supporting acceptance of the method.

A. Principle

The QuEChERS (quick, easy, cheap, effective, rugged, and safe) method uses a single-step buffered acetonitrile (MeCN) extraction and salting out liquid–liquid partitioning from the water in the sample with $MgSO_4$. Dispersive-solid-phase extraction (dispersive-SPE) cleanup is done to remove organic acids, excess water, and other components with a combination of primary secondary amine (PSA) sorbent and $MgSO_4$; then the extracts are analyzed by mass spectrometry (MS) techniques after a chromatographic analytical separation. Figure **2007.01** outlines the protocol in a box format. In brief, a well-chopped food sample along with 1 mL of 1% acetic acid (HOAc) in MeCN and 0.5 g anhydrous $MgSO_4$/NaOAc (4/1, w/w) per g sample are added to a centrifuge tube or bottle, which is shaken and centrifuged. A portion of the MeCN extract (upper layer) is added to anhydrous $MgSO_4$/PSA sorbent (3/1, w/w; 200 mg per 1 mL extract), mixed, and centrifuged. This final extract is transferred to autosampler vials for analysis by gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/tandem mass spectrometry (LC/MS/MS) to identify and determine a wide range of pesticide residues. To achieve <10 ng/g detection limits in modern GC/MS, large volume injection (LVI) of 8 µL is typically needed, or the final extract can be concentrated and solvent exchanged to toluene (4 g/mL), in which case 2 µL splitless injection is used.

Both GC/MS and LC/MS/MS techniques are prone to matrix effects in pesticide residue analysis, albeit for different reasons [Erney, D.R., Gillespie, A.M., Gilvydis, D.M., & Poole, C.F. (1993) *J. Chromatogr.* **638**, 57–63; Hajslova, J., & Zrostlikova, J. (2003) *J. Chromatogr. A* **1000**, 181–197; Alder, L., Luderitz, S., Lindtner, K., & Stan, H.J. (2004) *J. Chromatogr. A* **1058**, 67–79]. To account for these effects, matrix-matched calibration was conducted (calibration standards in solvent solution may also be used if matrix effects are shown not to occur). Due to the situation that some laboratories had LVI capability and others did not, the necessary amounts of matrix blank(s) and final extract volume was different for some laboratories than others. Depending on the water content of the matrix, a 15 g sample typically yields 11–14 mL of initial MeCN extract after centrifugation. In dispersive-SPE, roughly half of the extract is lost to the powders, thus about 6–7 mL of final extract can be expected for a 15 g sample. Two options were provided in the protocol to account for the different situations among the laboratories.

Table 2007.01A. Interlaboratory study results for incurred pesticides (and chlorpyrifos-methyl)

Analyte	Matrix	Avg. concn	s_r[a]	RSD_r[b], %	S_R[c], ng/g	Rec., %	RSD_R[d], %	HorRat	No. of labs	Outlier labs[e]
Chlorpyrifos-methyl	Grapes	165	14	8.5	35	83	21	1.00	11	6-C, 4-C
	Lettuces	178	20	11	30	89	17	0.81	10	11-SG
	Oranges	174	25	14	36	87	20	0.98	12	
Kresoxim-methyl	Grapes	9.2	1.9	21[f]	3.2	NA	35[f]	1.09	12	
Cyprodinil	Grapes	112	NA[g]	NA	18	NA	16	0.73	13	
λ-Cyhalothrin	Lettuces	58	6.1	11	11	NA	20	0.80	9	11-C
Permethrins	Lettuces	112	9.8	8.7	41	NA	36[f]	1.63	9	6-C, 1-C
Imidacloprid	Lettuces	12	NA	NA	1.6	NA	14	0.44	11	
Ethion	Oranges	198	23	12	36	NA	18	0.89	11	11-C
Thiabendazole	Oranges	53	3.8	7.2	7.6	NA	14	0.58	12	

AOAC SMPR® 2018.011

Standard Method Performance Requirements (SMPRs®) for Identification and Quantitation of Selected Pesticide Residues in Dried Cannabis Materials

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 stakeholder panels 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 study data for method being considered for *Performance Tested Methods*℠ or AOAC *Official Methods of Analysis*℠, and can be used as acceptance criteria for verification at user laboratories.

2 Applicability

Method, or a suite of methods, to identify and quantify selected pesticide residues (Table 1) in dried cannabis plant materials.

3 Analytical Technique

Any analytical technique(s) that measures the analytes of interest and meets the following method performance requirements is/are acceptable. More than one analytical technique may be needed.

4 Definitions

Dried plant material.—Dried whole or milled flower plant material from *Cannabis* sp. and its hybrids.

Limit of quantitation (LOQ).—Minimum concentration or mass of analyte in a given matrix that can be reported as a quantitative result.

Multiresidue method (MRM).—A method able to distinguish, followed by identification and/or quantification of, more than one pesticide residue in one analysis.

Recovery.—Fraction or percentage of spiked analyte that is recovered when the test sample is analyzed using the entire method.

Repeatability.—Variation arising when all efforts are made to keep conditions constant by using the same instrument and operator and repeating during a short time period. Expressed as the repeatability standard deviation (SD_r); or % repeatability relative standard deviation (%RSD_r).

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).

5 Method Performance Requirements

See Tables 2 and 3.

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.

7 Reference Material(s)

Refer to Annex F: *Development and Use of In-House Reference Materials* in Appendix F: *Guidelines for Standard Method Performance Requirements*, 21st Ed. of the *Official Methods of Analysis of AOAC INTERNATIONAL* (2019). Available at http://www.eoma.aoac.org/app_f.pdf

8 Validation Guidance

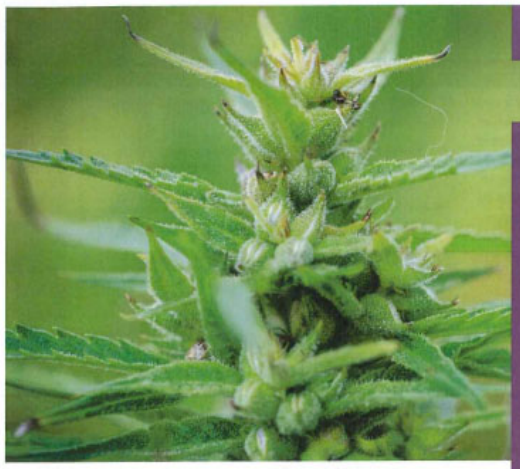
Appendix D: *Guidelines for Collaborative Study Procedures to Validate Characteristics of a Method of Analysis*, 21st Ed. of the *Official Methods of Analysis of AOAC INTERNATIONAL* (2019). Available at http://www.eoma.aoac.org/app_d.pdf

Appendix F: *Guidelines for Standard Method Performance Requirements*, 21st Ed. of the *Official Methods of Analysis of AOAC INTERNATIONAL* (2019). Available at http://www.eoma.aoac.org/app_f.pdf

Appendix K: *Guidelines for Dietary Supplements and Botanicals*, 21st Ed. of the *Official Methods of Analysis of AOAC INTERNATIONAL* (2019). Available at http://www.eoma.aoac.org/app_k.pdf

U.S. Food and Drug Administration, *Bioanalytical Method Validation Guidance for Industry* (May 2018)

European Commission Guidance Document on *Analytical Quality Control and Method Validation Procedures for Pesticide Residues and Analysis in Food and Feed* (SANTE/11813/2017)



APPLICATION NOTE

Liquid Chromatography/ Mass Spectrometry

Authors:

Ben Armstrong
Carl Carnagey

Juniper Analytics LLC
St. Bend, OR

Jingcun Wu
Sharanya Reddy
Joshua Ye
Feng Qin
Desmond Wichems
Charlie Schmidt

PerkinElmer, Inc.
Waltham, MA

Analysis of Pesticide Residues in Cannabis Regulated by Oregon State Using LC/MS/MS

Introduction

With the legalization of cannabis (marijuana) for medical and recreational applications ever increasing in more States in the US, the demand for clean and safe cannabis and related products has grown significantly. Like many other agricultural products, pesticides, antifungals, as well as performance enhancement reagents have been applied to cannabis to increase yields and reduce attacks from insects and mold. However, many of these chemicals and reagents may have harmful effects on humans, animals and the environment, especially to persons who grow or work with the products for a long time[1, 2]. In addition, when smoking plant materials such as tobacco and cannabis products, highly complex mixtures of compounds can be generated, many of which interact with the chemicals such as pesticides present in the initial product to form more toxic materials[3, 4]. It has been demonstrated that cannabis smoke contains significant amounts of pesticide residues when pesticides are initially present in the product[4]. Therefore, it is important to have a highly sensitive and selective testing method for the analyses of pesticides and other toxic chemicals such as mycotoxins to control the quality of the cannabis products and to evaluate the risk of human exposure. Although gas chromatography-mass spectrometry (GC-MS/MS) has been used for pesticide analysis in cannabis samples, it is not suitable for ionic and polar compounds, especially for compounds that are thermal labile in the GC injection port[5].

PerkinElmer
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Food and Environmental

SCIEX

Quantitation of Oregon List of Pesticides and Cannabinoids in Cannabis Matrices by LC-MS/MS

Diana Tran[1], KC Hyland[1], Simon Roberts[1], Scott Krepich[2], Paul Winkler[1], Craig Butt[1], and Christopher Borton[1]
[1]SCIEX, USA; [2]Phenomenex, USA

Increased legalization of cannabis for medical and recreational use substantiates the need for a standardized robust and reproducible method for quantitation of pesticide residues and relevant psychotropic cannabinoids in cannabis products. Pesticide application in agricultural industries is intended to protect crop yield from pests or pathogens. Insecticides, acaricides, fungicides or other protective chemical reagents on crops pose potential health risks both to field employees via exposure as well as consumers through consumption. Pesticides and pesticide action levels may be regulated differently by state. Currently, the most comprehensive list of pesticides and their respective MRLs allowed in plant products is known as the Oregon List of Pesticides.

Several pesticides on the Oregon List have been historically monitored by GC-MS including complicated sample preparation with derivatization and relatively long sample run times. Here, a fully verified LC-MS method is presented using two different SCIEX triple quadrupole mass spectrometers for the analysis of those pesticides comprising the Oregon Pesticide List.

The QET 4500 system presents a cost-effective platform for achieving the majority of the Oregon List Maximum Residual Limits (MRL) in cannabis flower matrix. The highly sensitive SCIEX Triple Quad™ / QTRAP® 6500+ system is capable of meeting the MRLs for the full list in cannabis flower matrix. Cannabis flower shows the most severe matrix- induced ion suppression on the target analytes and, therefore, the performance of this method in flower represents performance in the most difficult matrix.

The SCIEX vMethod Application for Quantitation of Pesticide Residues in Cannabis Matrices 1.0 provides a step by step SOP that is suitable for use for ISO 17025 compliance, acquisition methods with optimized source and analyte parameters as well as a quantitation method using MultiQuant™ Software.

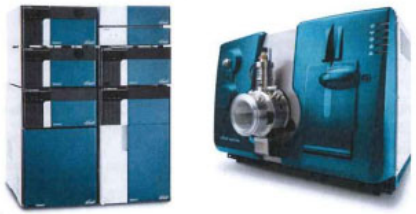

Figure 1: The SCIEX ExionLC™ AC HPLC System with the SCIEX QET 4500 LC-MS/MS System.

Key Features of Complete Solution

- A simplified sample preparation protocol complete with analysis of all 59 compounds (pesticides and cannabinoids) using electrospray ionization (ESI) and LC-MS/MS.
- A 16 minute gradient maximizes separation of endogenous isobaric interferences for pesticide analysis.
- A five-minute gradient separates all ten isobaric cannabinoids from each other and ensures precision of quantitative analysis.
- Dilution with six pesticide deuterated internal standards and two cannabinoid internal standards during sample preparation allows for maximization of recoveries for the most analytes as well as the ability to correct for analyte recovery efficiency
- Fast polarity switching on the SCIEX Triple Quad / QTRAP Systems enables monitoring of targets in both negative and positive polarities in a single fast method.

MA Regulations

Appendix A - Table 01
Method Reference Table

Analysis	Technology	Primary Reference(s)	Ancillary Reference(s)	Comment
Residual Solvents	GC/MS	• USP <467> Residual Solvents • USP <621> Chromatography • USP <736> Mass Spectrometry	• EPA 8260C*	*Consulted for additional GC-MS and Headspace specific objectives and details on quantitation
Residual Solvents	GC/FID	• USP <467> Residual Solvents • USP <621> Chromatography • USP <736> Mass Spectrometry	• EPA 8000D* • EPA 8015D	*Consulted for additional chromatography confirmation requirements
Pesticides	LC/MS/MS	• AHP (2013) • EPA 1694*		*The AHP does not discuss methodology for the most current limits of pesticides set by MDPH. EPA 1694 was consulted for LC/MS/MS specific objectives of contaminants
Metals	ICP/MS	• USP <233> • USP <232> • USP <2232>	• EPA 6020A*	*Consulted for additional ICP-MS specific objectives
Cannabinoids	HPLC (UV-Vis or DAD)	• AHP (2013) • UNODC (2009)	• EPA 548.1*	*Consulted for additional HPLC specific objectives

Pesticide, Fungicide, Herbicide and Growth Regulator Considerations:

- Adopt the 2015 Oregon list and safety limits initially until further info is obtained for Arizona samples.
- Adopt AOAC validated GC/MS and LC-MS/MS methods possibly with EPA Method support.
- Test the AOAC methods to see if herbicides can be added.
- If testing identifies the use of a banned pesticide or the improper application of a permitted pesticide, then that test batch shall be considered to have failed contaminant testing.

Residual Solvents

A.R.S. § 36-2803

E. “Beginning November 1, 2020, before selling or dispensing marijuana or marijuana products to registered designated caregivers, nonprofit medical dispensaries shall test marijuana and marijuana products for medical use to determine unsafe levels of microbial contamination, heavy metals, pesticides, herbicides, fungicides, growth regulators and residual solvents and confirm the potency of the marijuana to be dispensed.”

AHP Residual Solvents

Solvent Residues

Limits on solvents used in the manufacture of botanical products are established by the International Conference on Harmonization (ICH) (ICH 2011), with exceptions made for ethanol and acetic acid in products formulated to contain these substances (e.g., tinctures and vinegars). According to the ICH guideline, solvents are categorized in 3 classes. Class 1 includes known carcinogens, toxic substances, and environmental hazards such as benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, and 1,1,1-trichloroethane. These are to be avoided in the manufacture of herbal and/or pharmaceutical products. Class 2 and 3 solvents (Table 12) are distinguished based on their relative toxicity level. Limits established for permissible daily exposures (PDE) are determined individually for Class 2 solvents. Limits for Class 3 solvents are set at a general limit of 50 mg/day. In addition, the ICH guideline lists solvents for which no adequate toxicological data was found (Table 13) and requires manufacturers of pharmaceutical products that choose to use these solvents to supply justification for residual levels of these solvents in their final products. Petroleum ether, found in this group, is reportedly used in the production of hash oil (UNODC 2009).

Solvent extracted products made with Class 3 or other solvents, are not to exceed 0.5% residual solvent by weight or 5000 parts per million (PPM) per 10 gram of solvent-based product and are to be quantified according to the United States Pharmacopeia (USP <467>), Residual Solvents, Option 1. Higher concentrations may also be acceptable provided they are realistic in relation to safety, manufacturing, and good manufacturing practices.

Table 12 Permissable and restricted solvents in the manufacture of cannabis preparations

Class 2 solvents		Class 3 solvents
Solvent	Permissible daily exposure, mg/day	Permissible daily exposure: 50 mg/day
Acetonitrile	4.1	Acetic acid†
Chlorobenzene	3.6	Acetone
Chloroform*	0.6	Anisole
Cyclohexane	38.8	1-Butanol
1,2-Dichlorothene	18.7	2-Butanol
Dichloromethane*	6.0	Butyl acetate
1,2-Dimethoxyethane	1.0	tert-Butylmethylether
N,N-Dimethylacetamide*	10.9	Cumene*
N,N-Dimethylformamide	8.8	Dimethyl sulfoxide
1,4-Dioxane*	3.8	Ethanol*†
2-Ethoxyethanol	1.6	Ethyl acetate
Ethyleneglycol	6.2	Ethyl ether
Formamide	2.2	Ethyl formate
Hexane	2.9	Formic acid
Methanol*	30.0	Heptane
2-Methoxyethanol	0.5	Isobutyl acetate
Methylbutyl ketone	0.5	Isopropyl acetate
Methylcyclohexane	11.8	Methyl acetate
N-Methylpyrrolidone*	5.3	3-Methyl-1-butanol
Nitromethane*	0.5	Methylethyl ketone
Pyridine*	2.0	Methylisobutyl ketone
Sulfolane	1.6	2-Methyl-1-propanol
Tetrahydrofuran	7.2	Pentane
Tetralin	1.0	1-Pentanol
Toluene*	8.9	1-Propanol
1,1,2-Trichloroethene	0.8	2-Propanol
Xylene	21.7	Propyl acetate

* Listed as chemicals known to the state of California to cause cancer or reproductive toxicity under Proposition 65 (CAEP

Source: AHPA (2008); CAEPA (2013); ICH (2011); United States Pharmacopeia (USP 30-NF 25 2007).

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	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
2	**Analyte**	**ICH/USP**	**ICH, USP, AHP (mg/day) Class 2/3**	**OR**	**RI**	**AR**	**PA**	**ND**	**WA**	**MA**	**CA**	**MI and MO**		**MT**	**MD**	**IA**	**LA**	**NM**	**CO**	**OK**	**AK**	**HI**	**NV**	**MN**	**FL**	**NH**
3	NJ Top 12 Tested	**Class 1**	**Permissible Daily Exposure**	**µg/g**	**ppm**	**µg/g**				**mg/kg**	**ppm**	**ppm**		**ppm**	**ppm**	**ppm**	**ppm**	**ppm**	**ppm**			**ppm**	**ppm**	**ppm**	**ppm**	**allowed**
4		**(ppm)**	**50 mg/day x 100 = ppm**		**All**					**All**	**Cat 1/2**	**Inhalable**	**Other**						**per gram**							**solvents*** **
5	Acetone		5000	5000	5000	5000	5000	5000	5000	5000	5000	750	5000	5000				2000	<1000ppm	<1000						<500
6	Ethanol		5000	5000	5000	5000	5000	5000	5000	5000	5000	1000	5000		<5000	5000	5000		<1000ppm							***
7	Ethyl acetate		5000	5000	5000	5000	5000	5000	5000	5000	5000	400	5000	5000												
8	Heptanes		5000	5000	5000	5000	5000	5000	5000	5000	5000	500	5000	5000	<5000		500	1000	<1000ppm	<1000	<500	500	<500			<500
9	Hexane (or n-hexane)		290	290	290	290	290	290	290	290	290	50	290	290	<290		10	250	<60ppm	<60	<10	10		<290	500	
10	Methanol		3000	3000		3000	3000	3000	3000	3000	3000	250	3000	3000				1000								
11	Pentane		5000	5000	5000	5000	5000	5000	5000	5000	5000	750	5000	5000				800	<1000ppm	<1000				<3000		
12	Toluene		890	890	890	890	890	890	890	890	890	150	890	890	<890		1	800	<180ppm	<180	<1	1				
13	xylene (or total m,p,o)		2170	2170	2170	2170	2170	2170	2170	2170	2170	150	2170	2170	<2170		1	2000	<430ppm	<430	<1	1				
14	Acetic acid		5000				5000	5000	5000	5000																
15	Acetonitrile		410	410	410	410	410	410	410	410	410	60	410													
16	Anisole		5000				5000	5000	5000	5000																
17	1-Butanol		5000	5000	5000	5000	5000	5000	5000	5000																
18	2-Butanol		5000	5000	5000	5000	5000	5000	5000	5000																
19	Butyl acetate		5000				5000	5000	5000	5000																
20	Tert-Butylmethyl ether		5000				5000	5000	5000	5000																
21	Chlorobenzene		360		360		360	360	360	360																
22	Chloroform		60		60		60	60	60	60	1	2	60	2												
23	Cumene		70	70	70	70	70	5000	5000	70																
24	Cyclohexane		3880	3880	3880	3880	3880	3880	3880	3880				3880				1000								
25	Dichloromethane		600	600	600	600	600	600	600	600	1	125	600	600				500								
26	1,2-Dimethoxyethane		100	100	100	100	100	100	100	100																
27	N,N-Dimethylacetamide		1090	1090	1090	1090	1090	1090	1090	1090																
28	N,N-Dimethylformamide		880	880	880	880	880	880	880	880																
29	Dimethylsulfoxide		5000	5000	5000	5000	5000	5000	5000	5000																
30	1,4- Dioxane		380	380	380	380	380	380	380	380																
31	2-Ethoxyethanol		160	160	160	160	160	160	160	160																
32	Ethylene glycol		620(2014) 310(2019)	620	620	620	620	310	310	620																
33	Ethyl ether		5000	5000	5000	5000	5000	5000	5000	5000	5000	500	5000													
34	Isobutyl acetate		5000				5000	5000	5000	5000																
35	Isopropyl acetate		5000	5000		5000	5000	5000	5000	5000																
36	2-Methoxyethanol		50		50		50	50	50	50																
37	Methylacetate		5000				5000	5000	5000	5000																
38	3-Methyl 1-butanol		5000				5000	5000	5000	5000																

2015

TECHNICAL REPORT:
OREGON HEALTH AUTHORITY'S PROCESS TO DETERMINE WHICH TYPES OF CONTAMINANTS TO TEST FOR IN CANNABIS PRODUCTS, AND LEVELS FOR ACTION

Author
David G. Farrer, Ph.D.
Public Health Toxicologist

Oregon Health Authority
PUBLIC HEALTH DIVISION

Table 3. List of solvents and their action levels

Solvent	Chemical Abstract Services (CAS) Registry number	Action level (µg/g)
1,2-Dimethoxyethane	110-71-4	100
1,4-Dioxane	123-91-1	380
1-Butanol	71-36-3	5000
1-Pentanol	71-41-0	5000
1-Propanol	71-23-8	5000
2-Butanol	78-92-2	5000
2-Butanone	78-93-3	5000
2-Ethoxyethanol	110-80-5	160
2-methylbutane	78-78-4	5000*
2-Propanol (IPA)	67-63-0	5000
Acetone	67-64-1	5000
Acetonitrile	75-05-8	410
Benzene	71-43-2	2
Butane	106-97-8	5000*
Cumene	98-82-8	70
Cyclohexane	110-82-7	3880
Dichloromethane	75-09-2	600
2,2-dimethylbutane	75-83-2	290†
2,3-dimethylbutane	79-29-8	290†
1,2-dimethylbenzene	95-47-6	See Xylenes
1,3-dimethylbenzene	108-38-3	See Xylenes
1,4-dimethylbenzene	106-42-3	See Xylenes
Dimethyl sulfoxide	67-68-5	5000

Solvent	Chemical Abstract Services (CAS) Registry number	Action level (µg/g)
Ethanol	64-17-5	5000
Ethyl acetate	141-78-6	5000
Ethylbenzene	100-41-4	See Xylenes
Ethyl ether	60-29-7	5000
Ethylene glycol	107-21-1	620
Ethylene Oxide	75-21-8	50
Heptane	142-82-5	5000
n-Hexane	110-54-3	290
Isopropyl acetate	108-21-4	5000
Methanol	67-56-1	3000
Methylpropane	75-28-5	5000*
2-Methylpentane	107-83-5	290†
3-Methylpentane	96-14-0	290†
N,N-dimethylacetamide	127-19-5	1090
N,N-dimethylformamide	68-12-2	880
Pentane	109-66-0	5000
Propane	74-98-6	5000*
Pyridine	110-86-1	200
Sulfolane	126-33-0	160
Tetrahydrofuran	109-99-9	720
Toluene	108-88-3	890
Xylenes‡	1330-20-7	2170

USP Method

⟨467⟩ RESIDUAL SOLVENTS

INTRODUCTION

This general chapter applies to existing drug substances, excipients, and products. All substances and products are subject to relevant control of solvents likely to be present in a substance or product.

Where the limits to be applied comply with those given below, tests for residual solvents are not generally mentioned in specific monographs, because the solvents employed may vary from one manufacturer to another.

The objective of this general chapter is to provide acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. The chapter recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. This general chapter does not address solvents deliberately used as excipients, nor does it address solvates. However, the content of solvents in such products should

Draft AOAC Cannabis Specific Method Criteria

DRAFT AOAC SMPR 2018.XXX; Version 2, July 23, 2019

Method Name: **Identification and Quantitation of Selected Residual Solvents in Dried Cannabis Materials**

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 Stakeholder Panels 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 study data for method being considered for *Performance Tested Methods* or AOAC *Official Methods of Analysis*, and can be used as acceptance criteria for verification at user laboratories.

2. **Applicability**:
Method, or a suite of methods, to identify and quantify selected residual solvents (Table 1) in cannabis derivatives .

3. **Analytical Technique**:
Any analytical technique(s) that measures the analytes of interest and meets the following method performance requirements is/are acceptable. More than one analytical technique may be needed.

MA Regulations

Appendix A - Table 01
Method Reference Table

Analysis	Technology	Primary Reference(s)	Ancillary Reference(s)	Comment
Residual Solvents	GC/MS	• USP <467> Residual Solvents • USP <621> Chromatography • USP <736> Mass Spectrometry	• EPA 8260C* Needs 8000D	*Consulted for additional GC-MS and Headspace specific objectives and details on quantitation
Residual Solvents	GC/FID	• USP <467> Residual Solvents • USP <621> Chromatography • USP <736> Mass Spectrometry	• EPA 8000D* • EPA 8015D	*Consulted for additional chromatography confirmation requirements
Pesticides	LC/MS/MS	• AHP (2013) • EPA 1694*		*The AHP does not discuss methodology for the most current limits of pesticides set by MDPH. EPA 1694 was consulted for LC/MS/MS specific objectives of contaminants
Metals	ICP/MS	• USP <233> • USP <232> • USP <2232>	• EPA 6020A*	*Consulted for additional ICP-MS specific objectives
Cannabinoids	HPLC (UV-Vis or DAD)	• AHP (2013) • UNODC (2009)	• EPA 548.1*	*Consulted for additional HPLC specific objectives

Residual Solvents Considerations:

- Adopt Oregon's 2015 list and safety limits initially until further info is obtained for Arizona samples.
- Adopt USP validated methods with the support from EPA Methods and AOAC cannabis specific method criteria.
- If test batch is found to contain levels of any chemical that could be toxic if consumed, then the Department may determine that the test batch has failed contaminant testing.

Potency

A.R.S. § 36-2803

E. "Beginning November 1, 2020, before selling or dispensing marijuana or marijuana products to registered designated caregivers, nonprofit medical dispensaries shall test marijuana and marijuana products for medical use to determine unsafe levels of microbial contamination, heavy metals, pesticides, herbicides, fungicides, growth regulators and residual solvents and confirm the potency of the marijuana to be dispensed."

2 AHP Potency Methods

High-Performance Liquid Chromatography (HPLC) for the Determination of Major Phytocannabinoids in Cannabis

Gas Chromatography with Flame Ionization Detection (GC-FID) for the Quantitation of Phytocannabinoids

Figure 18 Representative HPLC chromatograms of cannabinoid standards (A at 11 µg/mL) and cannabis raw material (B)

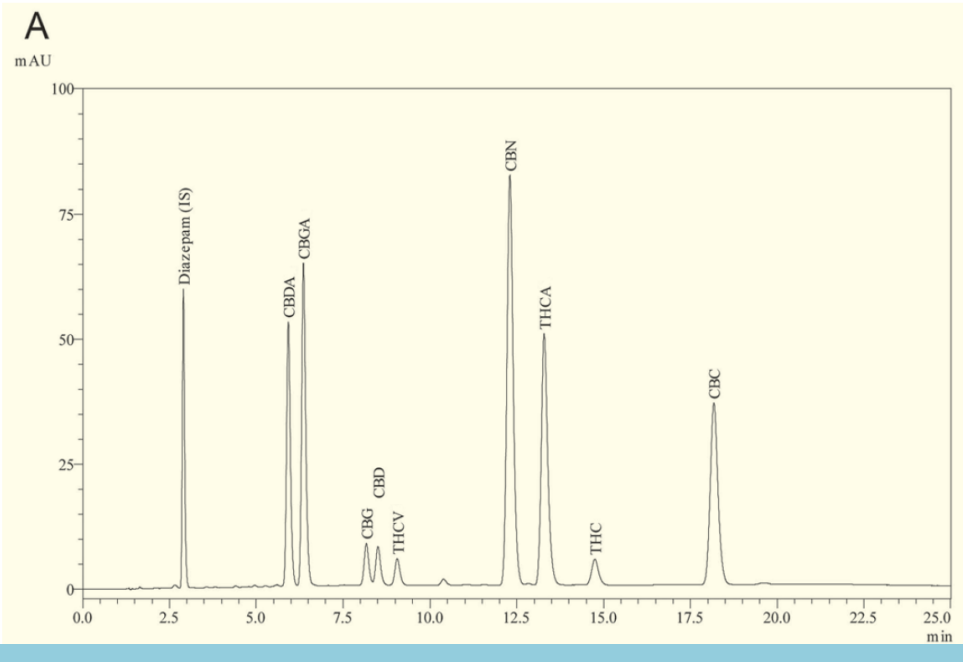
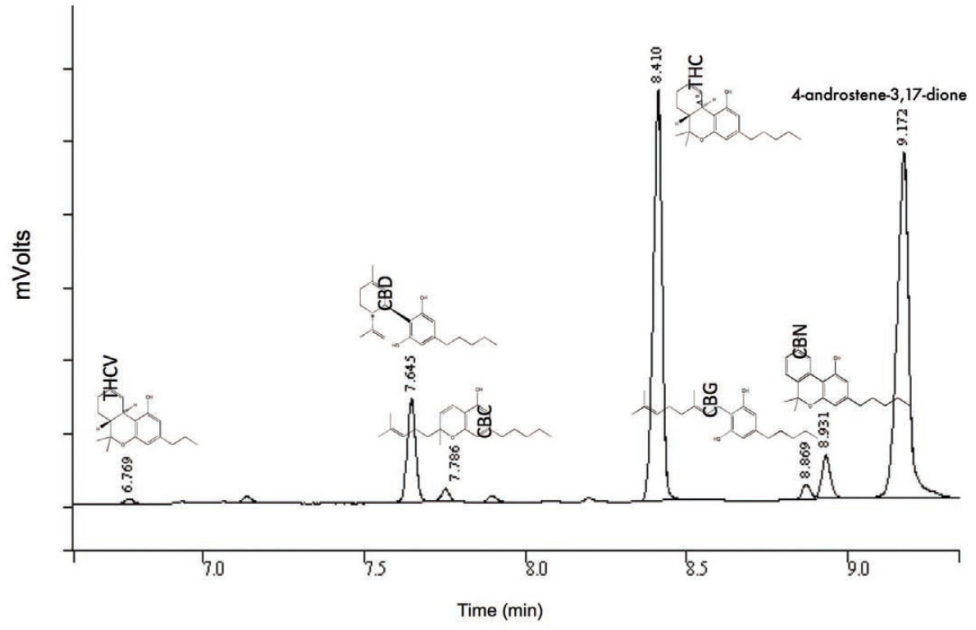


Figure 19 Characteristic gas chromatography (GC) chromatogram of cannabis with an internal standard



Potency Considerations:

- States' cannabinoid lists vary widely.
- Adopt AZ cannabinoid list that includes the acid forms THCa, CBDa and CBCa.
- Adopt method criteria for AHP methods with AOAC and EPA method support.

One Method Will Probably Not Work For All Matrices

Discussion of testing and potency standards

Next Meeting:
October 24, 2019

Adjourn