Nevada Cannabis Laboratory Association
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May 5, 2015

The Nevada Cannabis Laboratory Association (NVCLA) was formed on March 9, 2015 with the purpose to provide consistent analytical testing guidance for the cannabis industry in Nevada.

The NVCLA hereby provides the following recommendations to the Independent Laboratory Advisory Committee regarding Residual Solvents, Cannabinoid, and Terpenoid Testing:

Residual Solvent Testing

Per NAC 451A.654, solvent-based extracts of marijuana using n-butane, isobutene, propane, heptane, or other solvents or gases approved by the Division of at least 99 percent purity are to be screened for Residual Solvents. The Division has indicated that the list of solvents to be screened is specified in the American Herbal Pharmacopoeia, *Cannabis Inflorescence, Standards of Identity, Analysis, and Quality Control* (AHP) and has referenced the section on Solvent Residues and Tables 12 and 13 (Verbal communication between Yolanda Sinisgallo, NV Division of Public and Behavioral Health, and Benjamin Chew, MM Lab, January 21, 2015). Review of the AHP Monograph shows a need for clarification.

The AHP Monograph lists 4 Classes of solvents.

- Class 3 solvents are listed as having a Permissible Daily Exposure of 50 mg/day and state that Class 3 solvent limits are 0.5% (w/w).
- Class 2 solvents are listed with Permissible Daily Exposures, but no corresponding limits.
- Class 1 solvents are simply listed with no Permissible Daily Exposures or limits.
- While not specifically called a "Class", ten solvents are listed in Table 13 with "no adequate toxicological data available". Note that petroleum ether is a mixture of hydrocarbons and is difficult to quantify (or define as 99% pure). The two acids listed (trichloroacetic and trifluoroacetic) may require different methods to accurately quantify at low levels and would be detrimental to cannabis if used.

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While NAC 453A.654 specifies 99% pure solvents, it should be noted that technical grade solvents, which are often the least expensive options, are typically at least 99% pure, but there are usually no specifications on the final 1% of the solvent. For instance, technical grade acetone is usually 99.5%, but the rest of the mixture is often composed of other species that boil in roughly the same range as acetone. There are no specifications beyond 99.5%, and very often even the supplier does not know the exact composition. Hydrocarbons such as butane or heptane usually have many impurities of other hydrocarbons – multiple isomers of pentane, hexane, octane, etc. The impurities may have higher boiling points than the main solvent, and so depending on the procedure being used to strip the main solvent, higher boiling impurities may be concentrating in the extract.

The AHP references the International Conference on Harmonization, 2011. Impurities: Guidelines for Residual Solvents: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. No. Q3C(R5) (ICH).

The ICH guidelines provide options to translate Permissible Daily Exposure to sample concentration. Option 1 appears to be the most relevant:

Concentration (ppm) = 1000 x PDE / Dose

Dose = 5 grams/day, as determined by the ILAC at the April 1, 2015 meeting

PDE is Permissible Daily Exposure in mg/day

The ICH guidelines also state that quantitation is to be done if specific compounds are “likely to be present”. While a producer may not be intentionally using these solvents, there may be impurities in 99% pure solvents that may be concentrating in the extractions.

The following Proposal is submitted for consideration:

1. The Allowable Concentration limits for Class 3 solvents in a solvent-based extraction will be 0.5% (w/w), on an “as received” basis, as stated in the AHP Monograph.
2. Class 2 solvents tolerances will be converted from Permissible Daily Exposures to % (w/w) using Option 1 from the ICH and 5 grams/day dosage. Limits are on an “as-received” basis.

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Solvent	Permissible Daily Exposure (mg/day)	Allowable Concentration Limit (ppm)	Allowable Concentration Limit % (w/w)
Acetonitrile	4.1	820	0.082
Chlorobenzene	3.6	720	0.072
Chloroform	0.6	120	0.012
Cyclohexane	38.8	7760	0.776
1,2-Dichloroethene	18.7	3740	0.374
Dichloromethane	6.0	1200	0.120
1,2-Dimethoxyethane	1.0	200	0.020
N,N-Dimethylacetamide	10.9	2180	0.218
N,N-Dimethylformamide	8.8	1760	0.176
1,4-Dioxane	3.8	760	0.076
2-Ethoxyethanol	1.6	320	0.032
Ethylene glycol	6.2	124	0.124
Formamide	2.2	440	0.044
Hexane	2.9	580	0.058
Methanol	30.0	6000	0.600
2-Methoxyethanol	0.5	100	0.010
Methylbutyl ketone	0.5	100	0.010
Methylcyclohexane	11.8	2360	0.236
N-Methylpyrrolidone	5.3	106	0.106
Nitromethane	0.5	100	0.010
Pyridine	2.0	400	0.040
Sulfolane	1.6	320	0.032
Tetrahydrofuran	7.2	1440	0.144
Tetralin	1.0	200	0.020
Toluene	8.9	1780	0.178
1,1,2-Trichloroethane	0.8	160	0.016
Xylene	21.7	4340	0.434

3. Class 1 Solvents are listed in Table 1 of the ICH. It is suggested to adopt these levels. Note that 1,1,1-trichloroethane is an environmental hazard, not a health hazard.

Solvent	Allowable Level (ppm)	Allowable Level % (w/w)	Concern
Benzene	2	0.0002	Carcinogen
Carbon tetrachloride	4	0.0004	Toxic/Environmental
1,2-Dichloroethane	5	0.0005	Toxic
1,1-Dichloroethene	8	0.0008	Toxic
1,1,1-Trichloroethane	1500	0.1500	Environmental

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4. No toxicological data could be found for the following solvents:

1,1-Diethoxypropane
1,1-Dimethoxypropane
Isooctane
Isopropyl ether
Methylisopropyl ketone
Methyltetrahydrofuran
Petroleum ether
Trichloroacetic acid
Trifluoroacetic acid

It is recommended that these solvents not be allowed for use unless the producer supply justification to the Division. It should be noted that many of the solvents on this list will require significantly different methods to quantify (petroleum ether, trichloroacetic acid, and trifluoroacetic acid) from the other solvents and could represent significant cost for accurate quantitation. While these solvents may appear as impurities, unless they are intentionally being used by the producer, quantitative screening for them will not be performed.

Cannabinoid Testing

At a minimum, the following nine cannabinoids will be quantified by all labs:

Δ^9-Tetrahydrocannabinol (Δ^9-THC)
Δ^9-Tetrahyrocannabinolic acid (Δ^9-THCA)
Δ^8-Tetrahydrocannabinol (Δ^8-THC)
Cannabidiol (CBD)
Cannabidiolic acid (CBDA)
Cannabinol (CBN)
Δ^9-Tetrahydrocannabivarin (THCV)
Cannabigerol (CBG)
Cannabichromene (CBC)

While a lab is free to measure and report on additional cannabinoids, only these nine cannabinoids are subject to state proficiency testing.

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Terpenoid Testing

At a minimum, the following twelve terpenoids will be quantified by all labs:

α-Pinene
β-Pinene
β-Myrcene
Limonene
Terpinolene
cis-Ocimene
Linalool
β-Caryophyllene
Humulene
β-Eudesmol
Caryophyllene oxide
trans-Nerolidol

While a laboratory is free to measure and report on additional terpenoids, only these twelve terpenoids are subject to state proficiency testing.

Please do not hesitate to contact us if you have any questions.

Sincerely,

/s/ James Dean Leavitt
James Dean Leavitt

President, NVCLA