

The Challenges of Measuring Heavy Metal Contaminants in Cannabis Vaping Aerosols

Robert Thomas
Scientific Solutions

An educational white paper summarized from the author's new book, **Measuring Elemental Contaminants in Cannabis and Hemp**, CRC Press, Boca Raton, September, 2020, ISBN:9780367417376.

The recent announcement by the Colorado Marijuana Enforcement Division (CMED) proposed that by January, 2022 all marijuana concentrates in vaporized delivery devices must be tested for heavy metal contaminants in the emitted aerosol by an authorized testing facility. The metals must include, but are not limited to arsenic, cadmium, lead, and mercury (1). This has been long overdue, since it was first reported in 2017 that e-cigarette liquids were showing high levels of metals in the vaped aerosols (2). It caused some concern, but the problem wasn't fully investigated, except that the metals were likely coming from corrosion of some of the internal components. However the dangers of vaping resurfaced again in the Fall of last year (2019) when e-cigarettes and vaping pens were the source of almost 3000 hospitalizations and 70 deaths as a result of severe respiratory failure from vaping devices containing vitamin E acetate, one of the diluents used in electronic cannabis delivery systems (ECDS) (3). The problem eventually got resolved by removing this compound from the ingredients in all legal vaping products, although there is a possibility it could still be present in devices sold on the illicit market. Colorado has been very proactive in this field and as a result became the first state to require testing cannabinoid vaping aerosols for a panel of metals contaminants. This announcement has stimulated a great deal of interest from other state regulators to see how this eventually gets resolved.

This White Paper will take a closer look at the real-world, practical assessment of Colorado's intent to implement these new regulations and their implications for other states that will inevitably follow suit. It will begin by examining the fundamentals of vaping and the process of converting a vape liquid

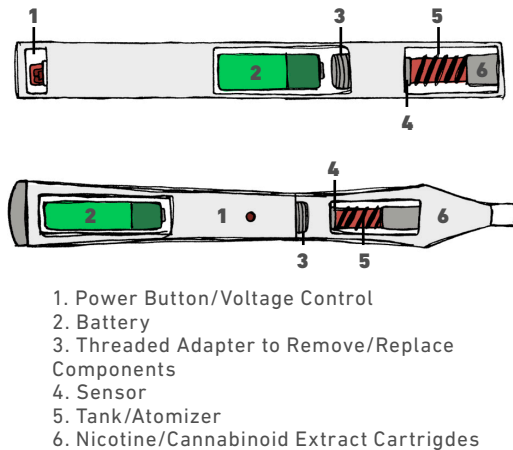
into an aerosol and the difficulties associated with characterizing the metal content. Next it will focus on the challenges of trapping and collecting the aerosol without contaminating the sample, and how best to validate the procedure using standard methods developed by the tobacco industry for electronic nicotine delivery systems (ENDS). And finally it will look at the ICP-MS measurement technique and the many potential sources of interferences observed when determining the most common metals found in vaping devices. It will also pose some questions and make suggestions to state regulators as to how the data could be used to regulate cannabis vaping devices.

Fundamentals of Vaping

Let's begin by first discussing the basics of vaping. When cannabis (extract or flower) is heated to 200-300°C in a cannabis vaping device, the psychoactive and therapeutic components such as THC, CBD and terpenes, volatilize into tiny airborne droplets that form an aerosol called a vapor, which is inhaled by the user. The process is carried out using a battery-powered heating element or atomizer to heat the cannabis product in a reservoir or tank that is often mixed with diluent liquids like propylene glycol, glycerin or medium chain triglycerides (MCT) to decrease its viscosity and flavoring agents to enhance the taste. In single-use or rechargeable cartridges, the liquid is often soaked into fibers and a heating element is wound around a wick. In pods, the liquid is in direct contact with the heating element within the pod. In tank or refillable systems, users add their desired liquid into a compartment. In some devices, the temperature can be selected using variable voltage control. As

a result, all of these variables make it extremely difficult to predict what metals are in the liquid and find their way into the aerosol. A schematic of two popular vaping pen designs are shown in Figure 1.

Figure 1: Basic components of two common cannabis vaping pens (www.glennaelisabeth.com)



Clearly there needs to be a way of testing these devices, but how realistic is it to expect cannabis testing labs to be well-versed in the very difficult analysis of characterizing vaping aerosols. There have been a number of reports in the public domain of E-liquids being analyzed (4) but very little has appeared on charactering aerosols. Although an exploratory pilot study was carried out on the traditional big four heavy metals of Pb, Cd, As and Hg which was presented at the 2019 CannMed Conference (5). We are not even sure what additional metals to test for, because there are myriad of designs out there with a variety of different internal parts. And clearly the components being used inside the device will dictate what metals are being corroded and transported to the consumer. For example, some of the common materials being used for tanks include plastic, glass (Si, Na, B) or stainless steel (Fe, Cr, Ni, Co, Mn), while coils and atomizers come in a variety of materials including nichrome (Ni, Cr), kanthal (Fe, Cr, Al), sometimes with brass electrical connectors (Cu, Zn) or other materials. Some of the newer atomizers are made from ceramic materials (Si, Al, Ca). Additionally, many modern vaping devices have variable voltages, allowing the user to select different vaping temperatures, based on the desired therapeutic or psychoactive effect. This means that if a higher temperature is selected, the amount and number of corroded metal particles being aerosolized could be significantly higher.

Characterizing Vaping Liquids for Heavy Metals

It's important to emphasize that the Colorado directives specifically stipulates characterizing the vaping aerosol for heavy metals, not just the liquid. Sampling an aerosol without contaminating the sample presents an order of magnitude greater complexity, because the aerosolization mechanism and transport of metallic particles at vaping temperatures around 200-300° C are very different to sampling metal ions in solution. Moreover, once the aerosol has been generated, there has to be a way to trap and collect the aerosol without additional metal contamination in order to measure its metal content using the analytical technique of choice - usually inductively coupled plasma mass spectrometry (ICP-MS). In comparison, sampling the vaping liquid is fairly straight forward, as it can just be sampled directly from the refillable pod or vaping device tank; although it should be emphasized that analyzing the liquid is not completely without its problems. The diluents used in the device will dictate what types of solvents to use for dilution. With nicotine systems, the diluents are typically propylene glycol and/or vegetable glycerin, which are hydrophilic (water soluble) in nature. This means that they can be extracted and dissolved using a nitric acid/hydrochloric acid mixture and as long as the calibration standards and blank are made up in a similar matrix, they can be presented to the ICP-MS for measurement of the required suite of elemental contaminants (6). However vaping devices used for cannabinoids are a little more complex to sample because propylene glycol and glycerol are used in some ECDS devices, but the diluents might also be mixtures that include vitamin E (tocopherol), and/or MCT oil which are hydrophobic (not water soluble) in nature. This of course is in addition to the cannabinoid extract itself which is oily and very viscous in nature. This means the liquid either has to be extracted and dissolved in an organic solvent, which will present problems for the ICP-MS instrument unless the appropriate desolvating/temperature-controlled sample introduction system (and perhaps oxygen addition) is used to reduce the likelihood of carbon being deposited on the interface cones. This requires an analyst with detailed knowledge and experience running organic samples, which if not carried out correctly, could lead to overheating of the interface and in extreme cases, melting of the interface cones. The alternative approach is to use a microwave digestion procedure using the appropriate acid mixture to oxidize the cannabis

extract and organic diluent and then redissolve the residue in a nitric/hydrochloric mixture, before being presented to the instrument for analysis.

Characterizing Vaping Aerosols for Heavy Metals

Let's now take a closer look at what is required to characterize electronic nicotine delivery systems (ENDS) or ECDS aerosols for trace metals. First it's important to emphasize that the transport of the metal particles in a vaping aerosol is not fully understood, but will be different based on the metal compositions of vaping device components and their heating characteristics. The temperatures at which ENDS/ECDS liquids are heated (200-300 °C) are insufficient for vaporization of most metals and metal oxides; therefore the mechanism of transport in the aerosol is likely to be independent of metal volatility (6). Moreover, limited entrainment of metal particles, or dissolved metal compounds in aerosol droplets formed by passage of air over the liquid surface is a possible metal transport mechanism. Another possible mechanism could involve aerosolization within liquid droplets sputtered from the heating element as the liquid boils and vaporizes. Note: aerosolization is the process of converting a substance into small particles, light enough to be carried on the air. As a result, the principal forms of the metals would not vaporize at the relatively low heating element temperatures, but rather be inefficiently entrained and transported in the aerosol (6, 7). For this reason, spiking trace elements into nicotine/cannabinoid liquids and measuring recoveries in the collected aerosol as a way of trying to validate the transportation, trapping and collecting method will unlikely be a useful exercise.

So first, it's important to understand that the standard method used to trap and collect the vapor from ENDS or ECDS is with an e-cigarette aerosol generation machine, which is an adaption of traditional mainstream smoking machines used to measure organic and inorganic contaminants in tobacco products like cigarettes and cigars. These aerosol generation testing machines work extremely well for measuring organic analytes but when it comes to evaluating inorganic pollutants they have limitations, because many of the components such as tubing, filters and impingers are not made out of high purity materials. As a result, measuring trace levels of elemental contaminants becomes very challenging, because of the potential for metals

to leach out of these materials when in contact with acids used for washing. For example, the standard filters used to trap the particulates from mainstream smoke or vapor are made from glass fiber, which is notoriously high in acid-leachable trace elements. In addition, the standard impinger is typically made from borosilicate glass, which again has acid leachable trace metals. Low purity quartz filters also have high levels of acid leachable metals and are not suitable as trapping materials for analysis of metals at low concentrations in ENDS and ECDS aerosols. Glass impingers should be replaced with metal-free perfluoroalkoxy resin (PFA). In addition, electrostatic precipitation units which are sometimes used in traditional smoking machines are not appropriate traps for aerosol collection. It should also be pointed out that the standard transfer tubes in these machines are typically made from tygon, which is known to contain acid-leachable metals. For that reason, either acid washed tygon tubing should be used with trapping devices, or better still, traps should consist of fluorinated ethylene propylene (FEP) or PFA tubing, which are considered higher purity polymers with respect to metals. So researchers who are interested in looking at very low levels of trace metals in e-cigarette aerosols typically have to customize the aerosol generation machines to make them better-suited for looking at trace metals. These issues become another layer of complexity for testing labs that are tasked with measuring low levels of heavy metals in ECDS aerosols.

E-Cigarette Aerosol Generation and Collection

If vaping aerosol analyses are to provide robust data, the methodologies and instrumentation must be scientifically sound and defensible. While no vaping machine puffing regimen mimics a human vaper, it is imperative that the data collected follows a standard and reproducible procedure. There is an ISO standard - Method, 20768:2018, which was specifically developed for the routine testing of vapor products with an analytical vaping machine (8). However there are no cited references in the public domain to understand how it is being applied to this type of analysis. So another standard method is CORESTA Method 81 (9), which defines the requirements for the generation and collection of e-cigarette aerosol for analytical testing purposes. It is similar in functionality to the ISO Method and has been widely used with acceptable specifications,

including prescribed limits for pressure drops, puff volume, puff time, and puff profile for generation and collection of reproducible ENDS aerosol results. In addition, there are many citations in the open literature on the use of CORESTA Method 81 for carrying out investigations of metal particulates in END systems, many of which are referenced in this article. The testing protocol described in the CORESTA method requires a 3 second; 55 mL puff every 30 seconds with a machine pressure drop no greater than 300 Pascal (Pa) and a pressure drop across the aerosol trapping assembly no greater than 900 Pa with a rectangular puff profile at a linear air flow of 140 mm/s. Since the heating elements of some ENDS and ECDS devices are activated by sufficient air flow, the heating elements in these devices will not generate aerosol until the air flow reaches the rate that triggers the heating element. Therefore, a rectangular puff profile is required and should be verified with a 1000 Pa restrictor in place. The sum of the times required for air flow through the device to ascend to 18.5 mL/s and to descend to baseline may not exceed 10% of the puff. This assures that air flow-activated heating elements begin heating at the beginning of the puff. It should also be emphasized that since CORESTA Method 81 was written assuming the use of standard glass fiber filters for trapping organic constituents of aerosols, they should be replaced with traps that are appropriate for inorganic aerosol constituents.

NOTE: However, it is important to emphasize that the CORESTA 81 Method was developed for tobacco and nicotine products, so the puff specifications reflect a typical cigarette smoker or END consumer. We know that cannabis consumers use ECDS very differently with regard to duration, volume, frequency, and number of puffs. For that reason, specifications must be developed specifically for cannabis vaping systems. to ensure the data can be validated under standardized testing conditions.

The major specifications described in CORESTA Method No 81 are shown in Table 1.

Table 1: Major specifications defined in CORESTA Method No 81 (9)

Puff Specification	Value
Puff Profile	Rectangular with a pressure drop device of 1000 Pa ± 50 Pa.
Profile Maximum Flow Rate	18.5 ml/s ± 1 ml/s
Puff Duration	3 s ± 0.1s
Puff Volume	55 ml ± 0.3 ml
Puff Frequency	1 puff every 30s
Puff Number	Total number of puffs collected from an e-cigarette

There are many different e-cigarette aerosol vaping systems on the market, which can accommodate multiple e-cigarettes or vaping devices and are suitable for ECDS. An example of one is shown in Figure 2 which is the Cerulean CETI 8 - an 8-port aerosol testing machine (10).

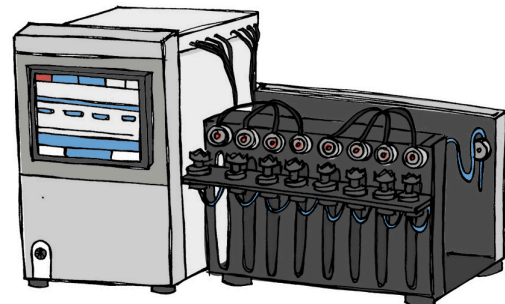


Figure 2: A typical 8-port aerosol testing machine (www.glennaelisabeth.com)

The weight of each element in nanograms (ng) in collected aerosol is then calculated based on the number of puffs. For example, a common unit to compare different ENDS or ECDS is either ng/10 puffs or ng/50 puffs, depending on the purpose of the analysis.

Collecting and Trapping Hydrophobic Liquids from ECDS

As mentioned previously, analyzing E-liquids from ENDS and ECDS is a fairly straight forward dilute and shoot method using a nitric acid/hydrochloric acid mixture, because diluents like propylene glycol and vegetable glycerin are water soluble. Even liquids from ECDS are not over complicated because the hydrophobic cannabinoid oils and diluents like MCT oil can either be diluted with a suitable organic solvent (as long as the sample introduction system is optimized) or the oils can be digested in a microwave digestion oven. Both these approaches are more time consuming but definitely achievable with an experienced analyst. However, to sample a hydrophobic aerosol of different oil mixtures is an order of magnitude more difficult. Filters tend to become clogged by viscous condensates. There is a good chance that the resulting collected material will be oily in nature which might require an organic solvent to make sure that will also maintain the metallic contaminants in solution.

This is exemplified by the trapping methodology described in a recent publication by Pappas and coworkers, which is based on a modification of the method used for ENDS (6, 11). The trap consists of a 518 cm length of 3.97 mm i.d. FEP tubing that is connected to the vaping machine syringe pump. This tubing is thoroughly rinsed with 2% v/v nitric acid + 1% v/v hydrochloric acid before and between each use. The vaping devices are connected to the FEP tubing from the vaping machine with tygon tubing that has been thoroughly soaked in 2% v/v nitric acid + 1% v/v hydrochloric acid, since untreated tygon has leachable metals. The FEP tubing traps aerosol and particles by condensation. The trapped aerosol is rinsed from the tubing with 3 x 8 mL rinses from a PFA (Perfluoroalkoxy) syringe with 2% v/v nitric acid + 1% v/v hydrochloric acid into a class A 25 mL polymethylpentene (PMP) volumetric flask, and dilution to 25 mL with the same acid solution. The modification of this method for oily ECD aerosols includes an initial tubing rinse with 5 mL diethylene glycol monoethyl ether (DEGMEE). This solvent has low volatility, is an excellent solvent for oils, and is water miscible. Unfortunately, no high purity grade with respect to trace metals is commercially available, so it must be distilled from a high purity fused silica quartz distillation flask prior to use, which would present difficulty with regard to regulatory analyses. DEGMEE dissolves and dilutes the oil droplets

from up to 50 CORESTA Method 81 vaping puffs as it passes through the condensation tube into a 50 mL PMP volumetric flask. The remnant in the condensation tube is then followed by 4 x 8 mL rinses with 2% v/v nitric acid + 1% v/v hydrochloric acid into the same 50 mL flask, and dilution to 50 mL with the same acid solution. Since DEGMEE is both oil and water miscible, it solubilizes or at least emulsifies the oil with the aqueous acid for analysis. Calibration standards are prepared in 2% v/v nitric acid, + 1% v/v hydrochloric acid + 10% DEGMEE for the purpose of matrix matching with the same solution obtained after rinsing aerosol metals from the condensation tube. **Note:** The data from this study used ng/50 puffs for comparison purposes.

What Analytes are Considered Important to Monitor?

As mentioned previously, metal components of ENDS and ECDS which could be exposed to the liquid inside the device cartridge or pod include stainless steel (mostly iron, chromium, and nickel), nichrome (nickel and chromium), kanthal (iron, chromium, and aluminum), brass (copper and zinc), and solder (tin and lead). Occasionally, wires are coated with silver and in some cases, silica-based ceramic heating elements are used as well as gold alloy coatings on electrical contacts.

Currently the regulated limits of the traditional “big four” heavy metals in inhaled cannabis products in the majority of the 36 US states where cannabis is legal are shown in Table 2 (12).

Table 2: Maximum Limits for Heavy Metal Contaminants in Inhaled Cannabis Products (12)

Heavy Metal	Maximum Limit (µg/g)
Pb	0.5
Cd	0.3
As	0.2
Hg	0.1

Maryland adds chromium (0.3), selenium (13.5), barium (34.3) and silver (0.7), while New York includes zinc (4000), antimony (2.0), copper (30), chromium (110) and nickel (2.0). (Note: all units are µg/g). So the question to ask is, what should be included in a panel of elements for ECDS aerosols?

Clearly the point of testing vaping devices is to find out what toxic substances are being corroded and transported to the user? However, can it be assumed that the vaping liquid (cannabinoid plus diluent oils) has been tested for at least the big four (lead, cadmium, arsenics and mercury) as part of the regulatory process in that state. I'm not sure this is always the case considering the many product recalls for CBD oils over the past 6-12 months (13). But assuming they have been tested for the state required panel and are below the maximum allowable limits, if any of these elements show up in the device aerosol, they will most probably have come from the vaping process. However, besides lead, which is a common constituent of solder, it is highly unlikely that components inside the device will contain elements like cadmium, arsenic or mercury, unless there has been some kind of contamination involved with sampling and/or measurement process. Of course that could happen, particularly if the optimum trapping and collection technology is not being used. So it would be legitimate to include all the likely metal candidates to the regulated list for the state, based on the design of the vaping device, but it is not clear what limits should be set for those additional elements. You could select, the United States Pharmacopeia/International Conference on Harmonization (USP/ICH) permitted daily exposure (PDE) limits for inhaled pharmaceuticals (14, 15), but they would be meaningless when current research on nicotine devices has shown that these metals are predominantly in the form of metal and metal oxide nanoparticles. Pappas and co-workers did a very thorough evaluation and confirmed this using scanning electron microscopy fitted with an energy dispersive X-ray spectrometer, together with dynamic light scattering and single particle ICP-MS studies (7).

Additionally, with an e-cigarette aerosol testing machine, how would the weight of metal per number of inhaled puffs, be compared with a traditional regulated maximum allowable limit? So for that reason, there would probably need to be an additional set of regulations just for ECDS, based on the nanograms per number of puffs. And one final point to emphasize, which is an ongoing problem in the field of cannabis testing. What measure of validation protocols would be appropriate? We know that it is not meaningful to spike the vape liquid and expect good recoveries, because the elements are not volatilized and transported consistently and efficiently to the trapping and collection device. So, at this point, it is not clear what could be used as a set of validation procedures for characterizing vaping aerosols for heavy metals.

Challenges in Measuring some Elements by ICP Mass Spectrometry

So up to now this series of articles has focused on the problem areas associated with sampling a representative aerosol from the liquid in the tank of the vaping system and how best to ensure that no contamination is occurring from the vapor testing machine. Let's now take a closer look at some of the major analytical challenges presented by measuring a multielement panel of analytes in vaping aerosols, containing high levels of carbon from the cannabinoid extract and organic diluents used. Note: For an educational primer on the major interferences in ICP-MS please refer to the following references (16).

The Big Four

Of the traditional big four heavy metals, arsenic and mercury are considered the most problematic for measurement by ICP-MS, while lead and cadmium are relatively straight forward to determine, because they are easily ionized, have very low detection limits, and, there are multiple isotopes available for quantitation with very few interferences. However, it should be emphasized that lead is by far the most likely to be present in vaping aerosols because of the possibility of leaded-solder used in the battery connectors or the use of lead in some brasses components to make them easier to machine (17).

So let's first take closer look at arsenic. It is monoisotopic at mass 75 amu, which suffers from a major interference from the $^{40}\text{Ar}^{35}\text{Cl}$ polyatomic ion at mass 75. So if there are any chloride (Cl^-) ions in the sample, detection at low levels becomes difficult. There are ways to reduce this interference using collision/reaction cell (CRC) technology by either utilizing a collision gas (helium) to reduce the $^{40}\text{Ar}^{35}\text{Cl}$ interference with kinetic energy discrimination or a reaction gas (such as oxygen) to mass shift ^{75}As to $^{75}\text{As}^{16}\text{O}$ at mass 91 for quantitation.

With regard to mercury, it's important to point out that when quantifying trace levels, the addition of approximately 1-2 ppm of gold (in the form of the chloride) may be necessary to stabilize the mercury to stop it being reduced to elemental mercury, which can be absorbed into the walls of the sample container or lost when the cap is removed. The excess gold competes with mercury for reducing substances in the samples, thus maintaining the mercury in oxidized mercuric ions which remain in solution. This is compounded if the solutions are left for extended periods of time before they are analyzed

(18). Having hydrochloric acid in the sample matrix is also beneficial to ensure there is an excess of chloride ions for coordination of mercury and moves the form of mercury away from the easily reducible mercuric ion to multichloro mercury complexes.

Different Metallic Components

As mentioned previously, if kanthal, brass, nichrome, stainless steel, soldered connectors or ceramic materials are used in the vaping system, it would seem appropriate to include aluminum, iron, chromium, copper, zinc, nickel, lead, tin and silicon as analytes, many of which are extremely challenging to determine in organic matrices by ICP-MS. In particular elements like aluminum, silicon and zinc are so environmentally ubiquitous that they are analytically challenging even using commercially-available ultrapure acids and high purity calibration standards. In addition, it is also very difficult to get clean blanks, which can severely compromise the detection capability. Another thing to consider is that an ICP-MS torch is made from quartz, which makes it very difficult to achieve a low silicon blank. Silicon also forms silicon oxide in the plasma that produces a refractory coating on sampler and skimmer cones. The buildup of the refractory silicon oxide on the cones causes a gradually increasing silicon background. In addition the major isotope of silicon is at mass 28 amu (92% abundant), where there is massive interference from the nitrogen dimer ($^{14}\text{N}^{14}\text{N}$) at mass 28. Mass 30, only 3.1% isotopic abundance, has a similar interference from $^{14}\text{N}^{16}\text{O}$. Mass 29 could be used, but it is only 4.7% abundant, so detection capability would be severely compromised compared to mass 28. One way around this would be to use “triple or multi quadrupole” ICP-MS technology using oxygen as a reaction gas to mass shift ^{28}Si to $^{28}\text{Si}^{16}\text{O}$ at mass 44 for quantitation. But this technology is relatively new and would be challenging for analysts with very little experience in working with the ICP-MS technique.

Iron, though not as ubiquitous as aluminum and silicon, can also be a problematic analyte unless utmost care is taken to avoid contamination. Additionally, the major isotope of Fe is at mass 56, where there is a major interference from $^{40}\text{Ar}^{16}\text{O}$ at mass 56. This interference can either be minimized using helium in a collision cell with kinetic energy discrimination or removed with ammonia (NH_3) using reaction chemistry. For this reason, iron may also be an element that could be a problematic choice for routine purposes by non-experienced laboratories. Chromium and nickel are not as environmentally

problematic as iron, but analysts should remove any external stainless steel ejectors from pipettes or autosampler probes prior to using them with acid solutions, or use pipettes that do not have steel pipette tip ejectors for trace metal analyses to prevent contamination issues. In addition, chromium and nickel are not straight forward to determine by ICP-MS. In particular chromium's major isotope is at mass 52 (84% abundant), where there is a massive polyatomic interference from $^{40}\text{Ar}^{12}\text{C}$ produced by the argon gas and the high level of organic compounds in the sample (cannabinoids and diluents such as propylene glycol, glycerine and/or MCT oils). A less abundant isotope could be used at either mass 53 or 54, but they are much less sensitive. A collision cell using helium will only have limited success of reducing the interference because of the organic matrices in vaping liquids. For that reason, measuring ultra-trace levels of chromium in an organic matrix might require a triple quadrupole technology using oxygen as a reaction gas to mass shift the ^{52}Cr and use $^{52}\text{Cr}^{16}\text{O}$ at mass 68 for quantitation. Note: Nickel is not as difficult as chromium, but the $^{40}\text{Ar}^{18}\text{O}$ polyatomic could potentially pose some problems for the major isotope of nickel at mass 58, especially when measuring trace levels.

Finally, tin presents some unique challenges in organic solvents, particularly when a heated spray chamber is being used. Because of the high volatility of Sn (IV) in the presence of hydrochloric acid it will be lost as a volatile tetrachloro complex before it enters the plasma and not be accurately measured. However, this can be compensated by adding a few mLs of 1% hydrofluoric acid to the sample, which converts the Sn (IV) to SnF_4 , which is less volatile. However, if laboratories are not well trained in safe handling of hydrofluoric acid, then it should not be used, and either tin should be eliminated from the list of analytes or a Peltier cooled spray chamber should be used in place of the higher sensitivity desolvating sample introduction system.

These are just a few examples of the many analytical challenges in characterizing ECDS aerosols for elemental contaminants by ICP-MS. Without question, carrying out quantitation of low-level impurities requires knowledge and experience of working in the ultra-trace environment, particularly when the sample matrix is organic in nature, that requires specialized sample introduction equipment. These are not insurmountable hurdles to overcome, but in light of the many novice users in cannabis testing labs who are not well versed in the complexities of the technique, these issues can easily lead to errors and inaccuracies that could result in false positive and false negative results.

Final Thoughts and Future Direction

It is hoped that this White Paper has provided a realistic assessment of the new Colorado regulations for the measurement of heavy metals in cannabis vaping aerosols. Its main objective is to help the analytical testing community who are tasked with carrying out this analysis to avoid pitfalls and improve analytical practices. The information is by no means exhaustive, but it is meant to give the reader an overview of what additional equipment is required and how best to optimize its operation to trap, collect and sample elemental contaminants from this complex sample matrix. In addition, it has offered guidance on how best to approach the quantitation of this panel of analytes with a more complete understanding of the strengths and weaknesses of ICP-MS for this type of sample matrix.

However, without knowing what an “average” vaper typically consumes per day or per week, it is very difficult to correlate the weight of heavy metals per inhalation (ng/number of puff) with the current regulations for inhaled cannabis products ($\mu\text{g/g}$). However an approximation can be made, using the weight of liquid in a typical vaping cart, the number of inhalations (puffs) of an average user and historical heavy metal data derived from electronic nicotine delivery (END) systems. So let’s take lead (Pb) as an example. A typical vaping cartridge contains approx. 0.5-1 g of liquid, which is equivalent to 150-250 puffs depending on the user (19). Based on evidence in a study by Halstead and coworkers at the CDC, who characterized 17 different END system for a suite of heavy metals, they found that for the majority of the systems Pb varied between 0.050 ng/10 puffs (Limit of Detection) and 3.3 ng/10 puffs, with a mean of 1.3 ng/10 puffs (with one flyer of 11.4 ng/10 puffs) (6). If we take the average number of puffs in a vaping device containing 1g of liquid to be 200, this correlates to 26 ng/g of Pb in one cartridge, or 0.026 $\mu\text{g/g}$. So based on most states’ inhalation maximum contaminant limits (MCL) for Pb to be 0.5 $\mu\text{g/g}$, an assessment could be made that a user would need to go through about 20 vapes or vape refills before they reached the MCL. Of course the timeframe would depend on what is considered a normal frequency of vaping.....someone who uses a vape refill every day would reach this in 20 days, while someone who’s vaping frequency is 1 per week, it would take them 20 weeks. Moreover, irrespective of whether it’s valid to make a comparison of the classic big 4 heavy metals in this way, it would be difficult to do it for the other metals found in vaping devices, because there are no state limits to compare them with. For that reason, perhaps there needs to be separate regulations specifically for vaping devices, because it is not immediately obvious how the

comparison can be made for all metals, based on the current state-based regulatory framework. It’s also important to emphasize that there were large variations in the data generated by the Halstead study (6), which is confirmation of the wide variability in the type of components and materials used in different vaping technology for both nicotine and cannabinoid delivery systems.

Unfortunately, we are trying to regulate cannabis vaping devices with very few standard or validated methods for guidance, although there is some preliminary work being carried out by the ISO standards group, as mentioned earlier (20). It would therefore be far better to scrutinize their quality before they enter the supply chain by carrying out basic testing procedures to ensure some kind of contaminant assessment. This would save a great deal of time and effort in trying to regulate products that in many cases are flawed when they reach the consumer. One approach is to use standardized toxicity leaching procedures which reproduce the potentially corrosive environment of liquids inside the vaping device over time. This can be something like MCT (medium chain triglycerides) oil which is commonly used as a diluent or weak acids like acetic or citric acid which simulates an approximate pH of the liquid (21). The vaping device components are typically wetted, by filling with the appropriate liquid and left for a fixed period of time (up to 24 hours) before they are analyzed for the selected suite of elements by ICP-MS. It would at least be a qualitative indicator of whether heavy metal contaminants are being leached from inside the device, which could also help to get a better understanding of their shelf life. This is particularly relevant for lead, because it is extremely toxic and is the only one of the classic big four heavy metals that we know is used in the manufacture of some vaping components, which could potentially pose a serious long term health hazard for users of vaping systems (22). Ambitious perhaps, but we have to find away to eliminate these “dubious” and often illicit products from finding their way into the market place. It might even encourage the industry to design vaping devices with more inert materials that are unlikely to corrode or even develop systems that are free of metal components.

In the meantime, it will be interesting to see how Colorado “figures out” these new regulations, because other states are watching closely and possibly looking to add this to their list of regulations in the near future. There might be more clarity over the next twelve months, but as there are currently no standard testing procedures for cannabis vaping devices, it will be interesting to see how the industry responds.

Further Reading

1. Colorado to Require Cannabis Vapor Testing by 2022, L. Bear-McGuinness, *Analytical Cannabis*, October 15, 2020, <https://www.analyticalcannabis.com/news/colorado-to-require-cannabis-vapor-testing-by-2022-312726>
2. Lead and Other Toxic Metals Found in E-Cigarette Vapors, P. Olmedo et. al., Johns Hopkins Bloomberg School of Public Health, February 7, 2017, <https://www.jhsph.edu/news/news-releases/2017/study-toxic-metals-found-in-e-cigarette-liquids.html>
3. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products, Center for Disease Control and Prevention (CDC) Website: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
4. Analysis of Toxic Metals in Liquid from Electronic Cigarettes, N. Gray et.al., *International Journal of Environmental Research and Public Health*, 2019;16: doi: 10.3390/ijerph16224450.
5. Heavy Metal Contaminants from Cannabis Vaporizer Cartridges: Valid Concern or Blowing Smoke? I. Afia, R. Weltman, K. Boyar, CannMed Conference, September 2019: https://www.researchgate.net/publication/336070263_Heavy_Metal_Contaminants_from_Cannabis_Vaporizer_Cartridges_Valid_Concern_or_Blowing_Smoke
6. Analysis of Toxic Metals in Electronic Cigarette Aerosols Using a Novel Trap Design, M. Halstead et.al., *Journal of Analytical Toxicology*, 2020;44:149–155.
7. Toxic Metal-Containing Particles In Aerosols from Pod-Type Electronic Cigarettes. R.S Pappas, et al., *Journal of Analytical Toxicology*, 2020; doi: 10.1093/jat/bkaa088.
8. ISO Method, 20768:2018, Vapor Products - Routine Analytical Vaping Machine - Definitions and Standard Conditions, https://webstore.ansi.org/Standards/ISO/ISO207682018?gclid=EAIaIQobChMI2r70-6Ls7AIVH0y1Ch329wcKEAAYASAAEgIQ_A_D_BwE
9. CORESTA Recommended Method Number 81, Routine Analytical Machine for E-Cigarette Aerosol Generation and Collection – Definitions and Standard Conditions, June, 2015, https://www.coresta.org/sites/default/files/technical_documents/main/CRM_81.pdf
10. Cerulean CETI 8 E-cigarette vaping instrument (8 Channel), <https://www.cerulean.com/en/solutions/product/ceti-8-range>
11. Measurement of Elemental Constituents of Vaping Liquids and Aerosols with ICP-MS. R.S. Pappas et al. in R.J. Thomas, *Measuring Heavy Metal Contaminants in Cannabis and Hemp*, CRC Press, 2020, ISBN 9780367417376.
12. The Status of US States' Legalization of Medical Marijuana, <https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/>
13. Regulating Heavy Metal Contaminants in Cannabis: What Can be Learned from the Pharmaceutical Industry? R. J. Thomas, *Analytical Cannabis*, June 30, 2020, <https://www.analyticalcannabis.com/articles/regulating-heavy-metal-contaminants-in-cannabis-what-can-be-learned-from-the-pharmaceutical-312494>
14. United States Pharmacopeia General Chapter <232> Elemental Impurities – Limits: First Supplement to USP 40–NF 35, 2017, <https://www.usp.org/chemical-medicines/elemental-impurities-updates>
15. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Q3D, (R1) – Guideline for Elemental Impurities, ICH Website: <https://www.ich.org/page/quality-guidelines#3-6>
16. Practical Guide to ICP-MS: A Tutorial for Beginners, Third Edition, R. J. Thomas, CRC Press, Boca Raton, FL, ISBN 9781466555433, (2014), <https://www.routledge.com/Practical-Guide-to-ICP-MS-A-Tutorial-for-Beginners-Third-Edition/Thomas/p/book/9781466555433>
17. Heavy Metal Contamination From Metal Vape Cartridges, J. McKeil, Rx Leaf, May 20, 2019, <https://www.rxleaf.com/heavy-metal-contamination-from-metal-vape-cartridges/>
18. Mercury Preservation Techniques, Environmental Protection Agency (EPA), March 2003, https://www.inorganicventures.com/pub/media/wysiwyg/files/mercury_preservation_techniques.pdf
19. CBD Dosages for Vape, Oil, Tincture, and More, Vaping 360 Website: <https://vaping360.com/learn/cbd-dosages/>
20. ISO Method, 20768:2018, Vapor Products - Routine Analytical Vaping Machine - Definitions and Standard Conditions, https://webstore.ansi.org/Standards/ISO/ISO207682018?gclid=EAIaIQobChMI2r70-6Ls7AIVH0y1Ch329wcKEAAYASAAEgIQ_A_D_BwE
21. Heavy Metals Contamination: Is Cannabis Packaging to Blame? R. Newman, *Analytical Cannabis*, February 20, 2020, <https://www.analyticalcannabis.com/articles/heavy-metals-contamination-is-cannabis-packaging-to-blame-312246>
22. Disposable Cannabis Vape Cartridges May Pose Latent Lead Exposure Risk, A. Cheadle, *Analytical Cannabis*, August, 27, 2020, <https://www.analyticalcannabis.com/news/disposable-cannabis-vape-cartridges-may-pose-latent-lead-exposure-risk-study-finds-312620>

Note: A more comprehensive discussion of this topic can be found in the author's recently published reference book, *Measuring Heavy Metal Contaminants in Cannabis and Hemp*, published by CRC Press. More information about the book can be found at the following link:

<https://www.routledge.com/Measuring-Heavy-Metal-Contaminants-in-Cannabis-and-Hemp/Thomas/p/book/9780367417376>

In addition, the author of this article organized a 1-day educational workshop on measuring heavy metals in cannabis by ICP-MS last year (2019) in conjunction with the Maryland Medical Cannabis Commission (MMCC) where Dr. Steve Pappas, the leader of the Tobacco Inorganics Group at the CDC gave a talk on the challenges of measuring elemental contaminants in vaping delivery systems. The entire workshop was videoed including Dr. Pappas's talk, which can be found at the link below:

<https://www.analyticalcannabis.com/articles/workshop-on-heavy-metals-in-cannabis-by-icp-ms-now-available-to-view-312735>

For more information about the importance of testing cannabis and cannabinoid products for elemental contaminants, please refer to the recently published White Paper in this magazine. <https://www.analyticalcannabis.com/white-papers/the-importance-of-measuring-heavy-metal-contaminants-in-cannabis-and-hemp-312957>