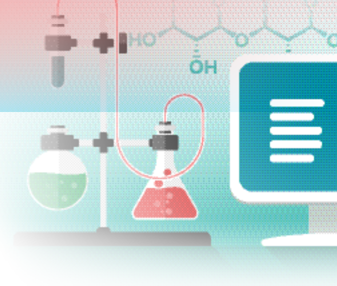


Beyond Potency: The Importance of Measuring Elemental Contaminants in Cannabis and Hemp

On a daily basis, the average person around the world is subjected to doses of heavy metals and other contaminants from a variety of sources. One of the most insidious sources of routes of exposure is through food, beverages, and other sources of oral consumption (that is, nutraceuticals, pharmaceuticals, and so on). The World Health Organization contends that food may be the source of the largest contribution to the intake of contaminants. Many agricultural products may naturally contain heavy metal and other contaminant compounds, from either natural biochemical processes or from bioaccumulation from the environment. Other products become contaminated by natural, agricultural, or industrial sources or poor hygiene methods of production and storage. Finally, there are food and beverage products that are intentionally adulterated or counterfeited with materials containing contamination. In this column, we look at different sources of potential contamination exposure that may be of concern to both the cannabis industry and the cannabis consumer from the perspective of an analytical industry professional with decades of experience in metals analysis. The guest author of this installment, Robert Thomas, has worked as an analytical chemist in the field of trace element analysis for more than 45 years, including 24 years for an inductively coupled plasma-mass spectrometry (ICP-MS) manufacturer and 19 years as principal of his own consulting company.

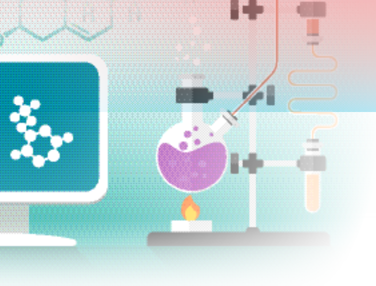
Robert Thomas

The cannabis and hemp industry is moving at such an alarming rate that the scientific and analytical testing community is struggling to keep up with it. It is estimated that the demand for medicinal and adult recreational cannabis-based products containing tetrahydrocannabinol (THC) and cannabidiol (CBD) compounds will exceed $25 billion in the U.S. by 2025 (1,2). However, because the U.S. Food and Drug Administration (FDA) has only been involved in this process when an investigational new drug (IND) has been submitted to conduct human clinical trials (for example, Epidiolex from GW Pharmaceuticals), regulating the industry to make sure products are safe for human consumption has been left to individual states. In addition, CBD-only products, which are dominating today's marketplace, are for all intents and purposes, unregulated by the federal government at this time.

Unfortunately, many of the state regulators (including state cannabis commissions and department. of agriculture personnel) do not have the necessary experience and background to fully understand all the safety, quality, and toxicological issues regarding the cultivation and production of cannabis and hemp products on the market today. Besides the need to characterize its potency (CBD and THC content) and other beneficial compounds, such as terpenoids, one of the most important contaminants to measure is the level of heavy metals because cannabis and hemp will avidly accumulate trace elements from the growing medium, soil, fertilizers, and even the metallic equipment used during the preparation and processing of the various concentrates and oils. This article, therefore, focuses on the importance of measuring elemental contaminants (heavy metals) in cannabis and hemp and, in particular, how they might be better regulated to ensure that products are safe for human medicinal and recreational consumption. It is universally recognized that the toxicity effects of heavy metals have been well-documented in the public domain because they have such a serious impact on human health, particularly for young children and adults with compromised immune systems (3,4). Note: Much of the information in this article has been sourced from my new book, *Measuring Heavy Metals in Cannabis and Hemp: A Practical Guide*, which will be published in the summer of 2020 (5).

Regulating Cannabis and Hemp

The lack of federal oversight with regard to heavy metals in medicinal cannabis and hemp products in the U.S. has meant that it has been left to the individual states to regulate its use. Medical



cannabis is legal in 34 states, while 12 states including the District of Columbia allow its use for adult recreational consumption (6). However, the cannabis plant is known to be a hyper-accumulator of heavy metals in the soil so it is critical to monitor levels of elemental contaminants to ensure cannabis products are safe to use (7). Unfortunately, there are many inconsistencies with heavy metal limits in different states where cannabis is legal. Some states define four heavy metals while others specify up to nine. Some are based on limits directly in the cannabis, while others are based on human consumption per day. Others take into consideration the body weight of the consumer, while some states do not even have heavy metal limits. Some states only require the measurement of heavy metals in the cannabis plant or flower, while others give different limits for the delivery method such as oral, inhalation, or transdermal (via the skin).

What Can be Learned from the Pharmaceutical Industry?

Clearly, there is a need for more consistency across state lines, particularly as the industry inevitably moves in the direction of being federally regulated. The cannabis industry can learn a great deal from the pharmaceutical industry, as it went through this process almost 25 years ago when it updated its 100-year-old semiquantitative (at best), sulfide colorimetric test for an undefined suite of heavy metals to eventually arrive at a list of 24 elemental impurities in drug products using plasma spectrochemical techniques. This new list included maximum permitted daily exposure (PDE) limits, based on well-established elemental toxicological data for drug delivery methods (including oral, parenteral, and inhalation), together with the analytical methodology to carry out the analysis.

These procedures were described in *United States Pharmacopeia* (*USP*) chapters 232, 2232, and 233 (8–10) for elemental impurities in pharmaceutical raw materials, drug compounds, and dietary supplements. This meant that pharmaceutical and nutraceutical manufacturers were required to not only understand the many potential sources of heavy metals in raw materials and active ingredients, but also to know how the manufacturing process contributed to the elemental impurities in the final drug products.

The beginning of the journey to regulate elemental impurities in pharmaceuticals in 1995 can be likened to the production of cannabis and hemp derived products today, where the source of elemental contaminants is not fully understood. In particular, the elemental toxicological guidelines to regulate the cannabis industry are being taken very loosely from a combination of methods and limits derived by the pharmaceutical, dietary supplements, food, environmental, and cosmetics industries. Even though the process of manufacturing cannabis products might be similar in some cases to drugs and herbal medicines, the consumers of cannabis and hemp products are using them very differently and in very different quantities, particularly compared to pharmaceuticals, which typically have a maximum daily dosage. The bottom line is that heavy metal toxicological data generated for pharmaceuticals over a number of decades cannot simply be transferred to cannabis, hemp, and their multitude of products.

An added complication is that the cannabis and hemp plant can not only absorb heavy metals from the soil, but also from contaminants in fertilizers, nutrients, pesticides, and the growing medium as well as from other environmental pathways (11). Additionally, the process of cutting, grinding, and preparing the cannabis and hemp flowers for extraction can often pick up elemental contaminants from the manufacturing equipment. Finally, the cannabinoid extraction process will extract different amounts of heavy metals, depending on the solvent or the super- and sub-critical extraction process used and could possibly end up in the finished products (12). It's also worth pointing out that the equipment used to deliver these products to consumers such as inhalers, vaporizers, and transdermal patches can mean the user is exposed to additional sources of elemental contaminants, apart from what's in the cannabinoid compound itself.

Phytoremediation Properties of Cannabis and Hemp

Cannabis and hemp are known to be hyper-accumulators of contaminants in the soil (13). That is why they have been used to clean up toxic waste sites where other kinds of remediation attempts have failed. In the aftermath of the Chernobyl nuclear melt down in the Ukraine in 1986, industrial hemp was planted to clean up the radioactive isotopes that had leaked into the soil and ground waters (14). Of course Chernobyl is an extreme example of heavy metal and radionuclide contamination, but as a result of normal human (anthropogenic) activities over the past few decades including mining, smelting, wood processing and treatment, electroplating, gasoline exhaust, energy production, use of fertilizers, pesticides, waste treatment plants, lead-based paint and plumbing materials, and so on, heavy metal pollution has become one of the most serious environmental problems today.

Phytoremediation using certain plants is emerging as a cost-effective technology to concentrate and remove elements, compounds, and pollutants from the environment. Within this field of phytoremediation, the use of cannabis and hemp plants to concentrate metals from the soil into the harvestable parts of roots and above-ground shoots (phytoextraction) has great potential as a viable alternative to traditional contaminated

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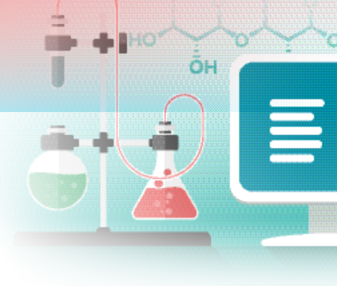

land remediation methods (15). However, the natural inclination of these plants to absorb heavy metals from the soil and growing environment could potentially limits its commercial use for the production of medicinal cannabinoid-based compounds. A number of studies have now been carried out on cannabis and hemp that provides convincing evidence that they are active accumulators of heavy metals such as lead, cadmium, arsenic, mercury, magnesium, copper, chromium, nickel, manganese, and cobalt, as the result of human activities (16).

Other Factors for Metal Uptake

The high concentrations of heavy metals accumulation achieved in cannabis cannot be explained exclusively by passive ion uptake. The hyper-accumulating properties of cannabis are dependent upon several factors including soil pH, availability of metal ions in solution, the nitrogen, potassium, and phosphorus nutrient content, and the ability of natural or added chelating compounds, such as humic acid and biochar, to bind with the heavy metals to stop them being taken up by the plant. These are some of the most important factors for the scavenging of heavy metals from the growing environment. It should also be noted that the plant's natural polyamine compounds (amino acid functional groups) will strengthen the defense response of plants and impact their activity against diverse environmental stressors including metal toxicity and oxidative stress.

Based on evidence in the public domain, there are about 15 heavy metals found in natural ecosystems (soil, water, air) that could be potential sources of contaminants accumulated by the plant including Pb, As, Hg, Cd, Ni, V, Co, Cu, Se, Ba, Ag, Sb, Cr, Mo, Mn, Zn, and Fe. Their levels of toxicity would need to be investigated further, but there is a case to be made that the majority of them could be the future basis of a federally-regulated panel of elemental contaminants in cannabis and hemp.

Potential of "Real-World" Sources of Metal Pollutants

With all the diverse and varied conditions used for growing cannabis, it is very difficult to eliminate all the potential sources of elemental contaminants to reduce their impact on the plant. However, it is well recognized that heavy metal pollution has been problematic over the past few decades, which if not minimized, can result in enhanced levels in cannabis and hemp. They might not all have a negative impact on the health of the plant during cultivation, but the chances that they will end up in the flowers and the final manufactured products are very high. It's therefore worth listing some of the many potential "real-world" sources of elemental contamination, both from a cannabis and hemp plant cultivation perspective as well as the cannabinoid manufacturing process.

Indoor and Outdoor Growing Sources

- Heavy metals in soil and growing media, particularly for plants that are cultivated outdoors
- Areas surrounding active or abandoned mines, particularly gold and silver mines that used mercury for extraction
- Poor water quality used in hydroponics for the growing of cannabis plants indoors (think of Pb-contaminated water in Flint, Michigan)
- Chromium, arsenic, and copper compounds used to treat and preserve wood
- Use of low-grade fertilizers or nutrients made from phosphate rocks, which contain significant amounts of heavy metals
- Inorganic pesticides that contain, arsenic, copper, lead, and mercury
- Emission of elemental mercury into the atmosphere from industries such as coal-fired power plants, metal refineries, petrochemical plants, and cement works (approximately 100 tons of Hg are emitted by U.S. industries annually)
- Decades of adding tetra ethyl lead to gasoline as an engine anti-knocking agent, which has ended up in the soil, particularly around major highways
- Decades of using lead, cadmium, and arsenic based pigments in paint

Manufacturing and Production Sources

- Manufacturing equipment used to produce the myriad of cannabis-based products such as stainless steel, plastic, polymers, and glassware
- Solvents and chemicals used to extract, infuse, and concentrate cannabinoids from the plants (super- or sub-critical extraction temperature and pressure will have an impact how much heavy metal is extracted into the final product)
- Leaching of heavy metals from delivery devices such as vaping sticks, inhalation devices, and infused transdermal patches
- Fillers and mineral-based raw materials added to tablet formulations
- Materials used in gelcap formulations
- Topical and transdermal cream formulations
- Recipe ingredients for edibles such as cookies and brownies
- Any products or ingredients sourced in Asia can potentially be a source of contamination (think melamine in infant formula and pet food, lead paint on toys, pewter in fake silver jewelry, and metallic components included Pb-based solder used in vaping devices to deliver products via inhalation)

The Smoking of Cannabis

It's worth pointing out that, historically, most consumers

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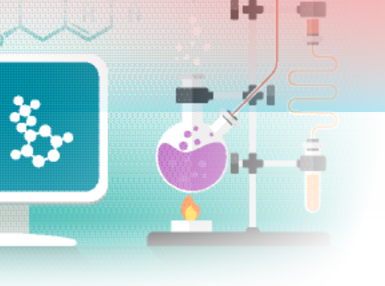


of recreational cannabis use it by the inhalation or smoking route. Smoke chemistry has been predominantly investigated in tobacco products, but many studies over the past 10 years have highlighted the qualitatively similar carcinogenic chemicals contained within both tobacco and cannabis smoke (17). In a recent study, the International Organization for Standardization and Health Canada analyzed tobacco and cannabis cigarettes. The heavy metals contained in both smoked products included: mercury, cadmium, lead, chromium, nickel, arsenic, manganese, and selenium (18). Quantitatively, there were lower heavy metal concentrations in cannabis smoke condensates, due mainly to the fact that the cannabis supply was grown hydroponically. In addition, the soil-less growth medium of the cannabis plants required water and water-soluble hydroponic vegetable fertilizers which contain nitrogen in the form of nitrates. So with no soil-based heavy metals to be extracted during the growth cycle of the cannabis, it was the liquid fertilizers used in the hydroponic systems that contributed mostly to the heavy metal levels. It should also be emphasized that in any hydroponic growing process, the elemental impurities in the water supply should be below the U.S. Environmental Protection Agency (EPA) maximum contaminant levels (MCL), otherwise the plant will pick up heavy metals from the water. This could be a real concern with old buildings that perhaps have been using lead pipes, or copper and iron pipes connected with lead-based solder. There is a great deal of information in the public domain about the uptake of heavy metals into tobacco and the resulting content in tobacco products, such as nicotine and electronic nicotine delivery (END) devices (19,20).

Testing Procedures

As a result of the high likelihood of heavy metals being present in hemp and cannabis products, the correct sampling and testing for heavy metals is absolutely critical. The most suitable and widely used technique is inductively coupled plasma-mass spectrometry (ICP-MS), which is a very sophisticated multielement analytical technique that can easily measure down to parts per trillion (ppt) detection levels. However, it requires an analytical chemist with a reasonably high level of knowledge and expertise to fully-understand the nuances of ultra-trace elemental analysis, including laboratory cleanliness, sources of contamination, sample preparation, digestion techniques, instrumental method development, interference corrections, calibration routines, use of reference materials, and validation procedures. In other words, in the hands of an inexperienced user it could easily generate erroneous results. For that reason, the expertise of the testing laboratory and the people running the instrumentation is of prime importance, and in particular to have an intimate knowledge of working in the ultra-trace environment and to be aware of all the potential sources of elemental contaminants outlined below (21).

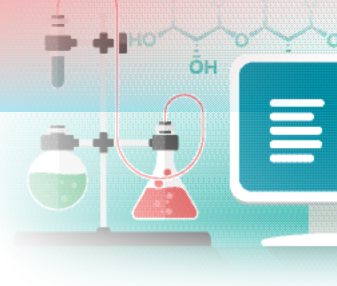
Sources from the Laboratory Testing Procedure and Methodology

- Cleanliness of sample preparation test area and equipment
- Laboratory dust or dirt of unknown origin (for example, old Pb-based paint)
- Cleanliness of sample digestion procedure
- Quality of the deionized water
- Purity of analytical reagents, acids, and solvents
- Impurities in laboratory glassware and plastic vessels or containers
- Purity of the plastic tubing used in delivering the sample to the instrument
- Contaminants from the analyst including clothing, cosmetics, lotions, perfumes, shampoo, jewelry, smoke
- Laboratory drywall or plasterboard walls and partitions made from flue gas desulfurization (FGD) waste products—some of these contain high levels of heavy metals because they have been made with "clinker" produced by scrubbing emissions from coal-fired power plants

I have become very familiar with the demands of the pharmaceutical community and, in particular, their trace element impurity requirements, so I have a very good perspective of how the industry approached the problem of tracing sources and pathways of heavy metals in raw materials and drug products. This topic was the focus of my most recent book entitled *Measuring Elemental Impurities in Pharmaceutical Materials: A Practical Guide*, which was published in the spring of 2018 (22). In the three years it took me to research and write this book, I realized the pharmaceutical manufacturing industry were not really familiar with ICP-MS, so they needed educating about how to generate high quality data when working at the ultra-trace level. After I published the book, on the suggestion from many people within the pharmaceutical or herbal supplements industries, I turned my attention to the cannabis and hemp industry and started interviewing cultivators, growers, producers, processors regulators, and testing laboratories to get a better understanding of what the industry needs with regard to its heavy metals' testing requirements. As a result of that background research, I have begun the process of writing the book, which will be entitled *Measuring Heavy Metal Contaminants in Cannabis and Hemp: A Practical Guide* (5).

Final Thoughts

Our environment has been severely polluted by heavy metals, which has compromised the ability of our natural ecosystems



to sustain and foster life. Heavy metals are known to be naturally occurring compounds, but anthropogenic activities introduce them in extremely large quantities into our agricultural growing and cultivation systems. Nowhere is this more evident than in the delicate balance of growing cannabis and hemp for commercial, medicinal, and recreational uses. Unfortunately, the demand for cannabinoid-based products is moving so fast that the scientific community is not keeping up with it; whether it's the testing of the products to make sure they are safe for human consumption or the medical research required to understand the biochemistry that is fundamental to treating a particular disease or ailment. The industry is both exciting and chaotic at the same time, but because of its unparalleled growth there appears to be very little incentive to bring in sensible regulations. There clearly needs to be a more comprehensive suite of elemental contaminants tested and to set the maximum limits on toxicological data based on the manner and the quantity that cannabis products are consumed. For that reason, researchers who are trying to raise the bar now will be rewarded when the FDA eventually starts to regulate the industry. However, in the meantime, I'm firmly committed to educating state regulators to better understand the potential sources of heavy metals in cannabis and hemp and to help the laboratory testing community improve the quality of its results.

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About the Guest Columnist

Robert Thomas is the principal of Scientific Solutions, a consulting company that serves the training, application, marketing, and writing needs of the trace element user community. He has worked in the field of atomic and mass spectroscopy for more than 45 years, including 24 years for a manufacturer of atomic spectroscopic instrumentation. He has served on the American Chemical Society (ACS) Committee on Analytical Reagents (CAR) for the past 19 years as leader of the plasma spectrochemistry, heavy metals task force, where he has worked very closely with the United States Pharmacopeia (USP) to align ACS heavy metal testing procedures with pharmaceutical guidelines. Rob has written almost 100 technical publications.

About the Columnist

Patricia Atkins
is a Senior Applications Scientist with SPEX CertiPrep and a member of both the AOAC and ASTM committees for cannabis.