Understanding Sources of Heavy Metals in Cannabis and Hemp: Benefits of a Risk Assessment Strategy

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The pharmaceutical industry took over 20 years to move from the semi-quantitative monitoring of a small group of heavy metals to finally arrive at regulations for 24 elemental impurities in drug products, listed by their permitted daily exposure (PDE) limits and categorized by toxicological impact and method of administration (oral, parenteral, inhalation, transdermal). The entire premise was based on carrying out a comprehensive risk assessment study of the elements' toxicity and the likelihood of finding them somewhere in the drug manufacturing process, which was fully documented in ICH Q3D guidelines for elemental impurities.

The cannabis industry cannot move beyond testing just four heavy metals until this type of risk assessment study is carried out. The objective of this white paper is to offer guidance as to which elemental contaminants are worthy of consideration, based on likely sources derived from the cultivation, extraction, processing, packaging and delivery of cannabis and hemp consumer products and to explore how this well-established pharmaceutical risk assessment process could be adapted by the cannabis industry.

The white paper will be broken down into four major sections outlined below:

1. The pharmaceutical risk assessment approach
2. Can risk analysis be adapted for the cannabis industry?
3. Sources of elemental contaminants derived from cultivation practices
4. Contributions from the cannabis extraction and manufacturing process

Part 1: What we can learn from the pharmaceutical industry

The lack of federal oversight with regard to heavy metals in medicinal and consumer cannabis products in the US has left individual states to regulate its use. Cannabis is legal in 37 states, while 18 states and Washington, DC, allow its use for adult recreational consumption[1]. 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. Unfortunately, there are many inconsistencies with heavy metal limits in different states where cannabis is legal. The vast majority of these states define the "big four" heavy metals: lead (Pb), arsenic (As), cadmium (Cd), and mercury (Hg).

New York State also requires the testing for chromium (Cr), nickel (Ni), copper (Cu), antimony (Sb) and zinc (Zn), while Michigan requires inorganic As (not total As) and also adds Cr, Ni, and Cu. Maryland, Missouri and a few other states also include Cr as well as the big four.

Some states base their limits directly in the cannabis, while others are related to human consumption per day. Others take into consideration the body weight of the consumer, while some states do not even have heavy metal limits. To complicate the situation, certain states only require heavy metals in the cannabis plant/flower, while some give different limits for the delivery method such as oral, inhalation, or transdermal[2]. These inconsistencies and the fractured nature of state-based limits would make it extremely complicated to implement at the federal level, because currently all regulations apply only in the state where the cannabis is grown, processed, and sold. And since the federal government still considers cannabis a Schedule I drug there can be no interstate commerce with regard to cannabis products. However, it is now legal to grow hemp anywhere in the US for the production of CBD-based consumer products, so it will be interesting to see how the Department of Agriculture regulates the hemp industry at the federal level, when cannabis is regulated by the individual states where it is legal.

Expanding the panel of elemental contaminants

So clearly there is a need for more consistency across state lines, particularly as the industry inevitably moves in the direction of federal oversight. This is further compounded by the fact that there is compelling evidence in the public domain that only monitoring the big four heavy metals is totally inadequate to ensure consumer safety. But how many metals should there be in an expanded list? At a recent ASTM workshop dedicated to the measurement of heavy metals in cannabis and hemp consumer products, compelling evidence was presented by a number of researchers that suggested 10- 15 elemental contaminants are worthy of consideration[3]. Moreover, the National Institute of Standards and Technology (NIST) is developing a 13-toxic element hemp certified reference material (CRM) through its CannaQAP Program to include Pb, Cd, As, Hg, beryllium (Be), cobalt (Co), Cr, manganese (Mn), molybdenum (Mo), Ni, selenium (Se), uranium (U), and vanadium (V)[4]. In addition, ASTM International's D37 Committee is in the process of developing a standardized ICP-MS method for up to 23 different elemental contaminants in cannabis (method currently going through the approval process). So, what will be a realistic panel of botanical heavy metals to monitor in cannabis consumer products, particularly as there is no comprehensive understanding of the sources of elemental contaminants in the cannabinoid production processes. Moreover, besides the big four, there is no consensus on the toxicity impact of other heavy metals in cannabis and hemp, as there has been no risk assessment study carried out with regard to heavy metal contaminants and for that reason, consumer safety is likely being compromised.

The only point of reference we have at this current time for what could be a federally regulated panel is the FDA approved CBD-based drug Epidiolex, which is available in the US to treat childhood seizures. Manufactured by UK-based GW Pharmaceuticals, it went through the regulatory process four years ago to get it approved in the US and had to show compliance by meeting permitted daily exposure (PDE) limits for up to 24 elemental impurities as defined in USP Chapter 232 and ICH Q3D guidelines. In fact, it's worth pointing out that the USP recently published for public comment in its pharmacopeial forum (PF 48-1), a draft monograph for CBD intended for use as an API for drug formulations, which stated that:

"Elemental impurities in official drug products are controlled according to the principles defined and requirements specified in Elemental Impurities—Limits 232, as presented in the General Notices 5.60.30."

In the long term, this could possibly indicate that the FDA will regulate CBD products for up to 24 elemental contaminants when it eventually has oversight of the cannabis industry. But more importantly, in the short term it implies that CBD being manufactured in the US for recreational or medicinal purposes is not pure enough for federally-approved drugs, because it only has to comply with the state's maximum limits for heavy metal contaminants, which in most US states is typically only Pb, Cd, As, and Hg. However, it's important to stress that a panel generated by pharmaceutical regulators isn't necessarily one that should be used by the cannabis industry, as the process for manufacturing cannabinoids is very different to drug products. So, the objective of this white paper is not necessarily to provide evidence as to what elemental contaminants the industry should be monitoring, but to offer guidance on which ones are worthy of consideration by implementing a comprehensive risk assessment study supported by evidence from information in the public domain and other sources about what metals are likely candidates.

Lessons from the pharmaceutical industry?

Image credit: Glenna Thomas.

The cannabis industry can learn a great deal from the pharmaceutical industry, as it went through this process over 20 years ago when it updated its 100-year-old semi-quantitative sulfide precipitation colorimetric test for a small suite of heavy metals to eventually arrive at a list of 24 elemental impurities in drug products defined as permitted daily exposure (PDE) limits and classified by their toxicity and the probability of inclusion in the drug product.

These procedures were described in United States Pharmacopeai Chapters 232 - Elemental Impurities[5] and 233 – Procedures[6] together with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3D guidelines on elemental impurities[7].

Note: The ICH is an international consortium of pharmaceutical regulatory authorities and pharmaceutical industry groups to discuss scientific and technical aspects of pharmaceuticals and develop guidelines.

These new guidelines defined maximum PDE limits based on well-established elemental toxicological data for drug delivery methods (including oral, parenteral, inhalation, and transdermal), together with the analytical methodology using techniques such as plasma spectrochemistry to carry out the analysis. This meant that pharmaceutical 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 the late 1990s can be compared to the production of cannabis and hemp derived products today, where the sources of elemental contaminants, the toxicological impacts of the contaminants and the methodology to perform the measurements were not fully understood or developed. 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 cannabinoids might be similar in some cases to drugs and herbal medicines derived from natural products, 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. So, let's take a more detailed look at how the pharmaceutical industry approached bringing in comprehensive regulations using a risk assessment approach of those elements that are not only known to be toxic but also likely to be potentially found somewhere in the drug manufacturing process.

The pharmaceutical risk assessment approach

ICH Q3D recommends that manufacturers conduct a product risk assessment by first identifying known and potential sources of elemental impurities. Manufacturers should consider all potential sources of

elemental impurities, such as elements intentionally added, elements present in the materials used to prepare the drug product, and elements introduced from manufacturing equipment or container closure systems. Manufacturers should then evaluate each elemental impurity likely to be present in the drug product by determining the observed or predicted level of the impurity and comparing it with the established PDE. If the risk assessment fails to show that an elemental impurity level is consistently less than the control threshold (defined as being 30 percent of the established PDE in the drug product), additional controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product. These additional controls could be included as in-process controls or in the specifications of the drug product or substance.

Benefits of using risk assessment

Rather than routinely testing drug products against a broad specification for elemental impurities, which may cause delays in product delivery, correct use of the risk assessment process will ensure that targeted and appropriate testing of materials will be performed where control is needed, and this creates the possibility that the manufacturer will be able to:

- Test for specific metals only.
- Test occasional batches or lots.
- Require minimum testing post approval.

This scientific-based and data-driven risk assessment ensures that the control strategy is appropriate and does not impact the product quality or patient safety.

Performing risk assessment

The first thing that is needed before starting the risk assessment is the route of administration and dose range for the product since the systemic exposure of the human system to elemental impurities varies with the route of administration: oral, inhaled, parenteral, or transdermal. In addition, some metals exhibit higher toxicity in some forms of administration than others. This type of information is shown in Table 1, which is taken from the most recent ICH Q3D (R1) and (R2) guidelines[7, 8].

From these data, it can be determined what the maximum limits will be for the product provided it has an oral, parenteral, inhaled, or transdermal administration.

Note: Transdermal (via the skin) PDEs were not included in the first draft of this guideline but are currently going through the review and approval process and are included here for information purposes only.

It's also important to emphasize that these are maximum limits per day. So, to calculate the allowable limit in the drug, these data must be divided by the recommended dosage for that drug. For example, if 10 grams (g) per day is the maximum dose these values must be divided by 10 to calculate the concentration in microgram per gram (µg/g) in the drug material. From these PDE data the control threshold can be calculated for any element that is considered worthy of a risk assessment.

Table 1: ICH Q3D (R2) guidelines for elemental impurities (7, 8)

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (µg/day)	Proposed Transdermal PDE (µg/day)
Cd	1	5	2	3	20
Pb	1	5	5	5	50
As	1	15	15	2	30
Hg	1	30	3	1	30
Co	2A	50	5	3	50
V	2A	100	10	1	100
Ni	2A	200	20	6	200
Tl	2B	8	8	8	8
Au	2B	300	300	3	3000
Pd	2B	100	10	1	100
Ir	2B	100	10	1	100
Os	2B	100	10	1	100
Rh	2B	100	10	1	100
Ru	2B	100	10	1	100
Se	2B	150	80	130	800
Ag	2B	150	15	7	150
Pt	2B	100	10	1	100
Li	3	550	250	25	2500
Sb	3	1200	90	20	900
Ba	3	1400	700	300	7000
Mo	3	3000	1500	10	15000
Cu	3	3000	300	30	3000
Sn	3	6000	600	60	6000
Cr	3	11000	1100	3	11000

How are the PDEs calculated?

Acceptable exposure levels for elemental impurities were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals and the methods adopted by International Program for Chemical Safety (IPCS) for assessing human health risk of chemicals[9]. These are very similar to the US EPA's Integrated Risk Information System[10], and the FDA's Guidance for Industry: Toxicological Principles for the Safety Assessment of Food Ingredients[11] and are based on the most relevant animal studies using the following calculation:

PDE = NO(A)EL x Mass Adjustment/Modifying Factors [F1 x F2 x F3 x F4 x F5]

Where...

NO (A)EL is No-Observed Adverse Effect Level as defined by IUPAC as the greatest concentration or amount of a substance, found by experiment, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

Mass adjustment is based on an arbitrary adult human body mass for either sex of 50 kilograms (kg). This relatively low mass provides an additional safety factor against the standard masses of 60 kg or 70 kg that are often used in this type of calculation.

Modifying Factors (F1-F5) are individual factors determined by professional judgment of a toxicologist and applied to bioassay data to relate the data to human safety.

Example of a PDE calculation

As an example, consider a toxicity study of cobalt in humans. The NOAEL for polycythemia (a blood cancer that increases the number of red blood cells in the body) is 1 milligram per day (mg/day). The PDE for cobalt in this study was calculated as follows:

PDE = 1 mg/day /[1 x 10 x 2 x 1 x 1] = 0.05 mg/day= 50 µg/day

Where...

F1 = 1 study in humans
F2 = 10 to account for differences between individual humans
F3 = 2 because the duration of the study was 90 days
F4 = 1 because no severe toxicity was encountered
F5 = 1 because a NOAEL was used

This is an example of how the PDE for cobalt has been calculated, but every elemental impurity in each of the four routes of administration defined in ICH Q3D will have a PDE maximum limit defined in µg/day, which is based on well-established animal studies. Detailed information about the toxicity of each elemental impurity, together with how the PDEs were calculated are included in these guidelines. As a result, every element in Table 1 will be categorized by its toxicity classification and the likelihood of finding it somewhere in the drug manufacturing process. So, let's take a closer look at these elemental classifications.

Elemental classification

With knowledge of the route of administration the information in Table 1 allows us to refine the number of elements that should be considered in a risk assessment study since most elements not used in the process may be discounted. This is due to the very low risk of certain elements being present unexpectedly in raw materials and process equipment due to their low abundance in natural sources. At a high level, risk is assessed as a combination of the toxicity of the element and its likelihood of occurrence, along with its likelihood of detection (simply stated: you won't find it if you don't look).

Class 1 and 2A metals, Pb, Cd, As, Hg, Co, V, and Ni must always be assessed irrespective of the route of administration. However, this does not mean they must be routinely tested for in an approved product, rather that data should be collected during the assessment phase to determine whether they are likely to occur in the finished product at levels at or near the PDE.

Class 2B metals, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, and Pt have a reduced probability of occurrence related to their low abundance and as a result, can be excluded unless they are intentionally added during the manufacture of the drug product. An example of Class 2B would be platinum group metals, which are used as catalysts in the organic synthesis of certain drugs.

Class 3 metals, Li, Sb, Ba, Mo, Cu, Sn, and Cr have relatively low toxicities by the oral route of administration but could warrant serious consideration for inhalation and intravenous routes, as discussed in detail in ICH Q3D.

ICH Q3D provides a clear structure for companies to follow in designing their risk assessment process, which is summarized as a fishbone diagram with the most common routes of potential contamination shown in Figure 1.

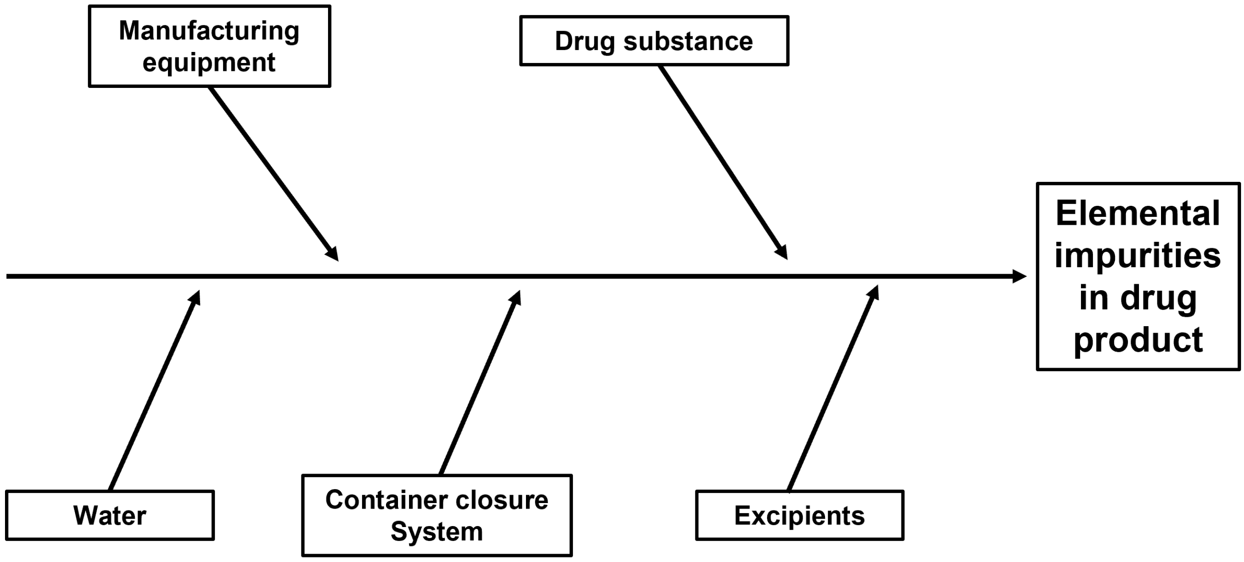

Figure 1: ICH Q3D Risk Assessment Fishbone Diagram.

Potential sources of elemental impurities

There are five likely routes for the introduction of elemental impurities, so if these inputs are well characterized and considered to be "clean" with respect to the relevant elemental impurity limits then the drug product will be acceptable without testing for elemental impurities. The ICH has provided pragmatic guidance as follows.

The applicant's risk assessment can be facilitated with information about the potential elemental impurities provided by suppliers of drug substances, excipients, container closure systems, and manufacturing equipment. The data to support this risk assessment can come from a number of sources that include, but are not limited to:

- Prior knowledge.
- Published literature.
- Data generated from similar processes.

- Supplier information or data.
- Testing of the components of the drug product.
- Testing of the drug product.

In summary, testing is not the mandated requirement, but data are absolutely critical. This means that as a company becomes more familiar with the elemental impurity risk assessment process, they will be able to leverage information gained in the development of previous products enabling them to streamline the process. Similarly, as information is published in the scientific literature the reliance on analytical testing will be reduced. If we consider the five sources of elemental impurities, it is clear that some are more likely to problematic than others. In order of complexity, they are: water, manufacturing equipment, container closure system, drug substance and excipients. Let's take a closer at each of these areas.

Water

ICH Q3D states "The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the process." In practice monitoring of water purification is a focus of FDA facility audits and therefore, as long as no significant changes to the quality of the water supply to the site occur, it is unlikely that the purification process supporting the claim of compliance to pharmacopeial standards will fail to also control unwanted elemental impurities. As long as these requiremnets are met, water can be used without testing for elemental impurities. For pharmaceuticals, the rationale for the acceptability of USP Purified Water is presented in a Pharmacopeial Forum Stimuli for Revision article in PF39(1) – Elemental Impurities in Pharmaceutical Waters, p.434.

Manufacturing equipment

The risk of inclusion of elemental impurities can be reduced through process understanding, equipment selection, equipment qualification, and good manufacturing practice (GMP) processes, as called out in Q3D:

"The specific elemental impurities of concern should be assessed based on knowledge of the composition of the components of the manufacturing equipment. The assessment of this source of elemental impurities is one that can be utilized potentially for many drug products using similar process trains and processes."

It can be argued that a specific plant configuration could be qualified for elemental impurity leaching by testing the qualification batches produced as part of the new drug application (NDA) submission process and that subsequent process using that configuration will not need test data provided that the reagents are not significantly different.

Container closure systems

This term refers to all the packaging components potentially contacting the drug product. It is known that packaging components can leach impurities and manufacturers have to provide studies on extractables and leachables as part of the product registration. ICH Q3D provides the following guidance:

"The probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system into the drug product during the shelf-life of the product. Studies to understand potential extractables and leachables from the final/actual container closure system should be performed (Q3D)."

There are two very useful publications by Jenke and co-workers on elemental impurities that can be used in the risk assessment Process[12, 13] and these studies by pharmaceutical industry experts cover a wider range of elements than those covered by ICH Q3D in over 100 test articles. The information provided can be used in the elemental impurity risk assessment process by providing the identities of commonly reported elements and data to support probability estimates of those becoming elemental impurities in the drug product. Furthermore, recommendations are made related to establishing elements of potential product impact for individual materials.

Drug substances

Drug substance manufacture uses catalysts that are a known potential contaminant and will have a control strategy in place as part of the process development, so are considered low risk but may have input materials that have non-GMP precursors and therefore provide a high risk of introducing unexpected elemental impurities.

Excipients

ICH Q3D explains that "Elemental impurities are often associated with mined materials and excipients. The presence of these impurities can be variable, especially with respect to mined excipients, which can complicate the risk assessment. The variation should be considered when establishing the probability for inclusion in the drug product."

Excipients sourced from plants (cellulose, for example), mined (talcum powder) or from animals (lactose and gelatin) can potentially be contaminated through man-made pollution or natural sources, particularly with As, Cd, Hg, and Pb and other heavy metals.

It is considered that highly refined excipients are low risk with respect to elemental impurities; examples are cellulose and lactose. However, data shows that elevated levels of class 1 and 2A metals are commonly encountered in mined excipients such as talcum powder and calcium carbonate, so these should be considered a high risk.

A paper on elemental impurities in excipients was published in Pharmaceutics, Drug Delivery and Pharmaceutical Technology which reported testing of 190 samples from 31 different excipients and 15 samples from eight drug substance provided through the International Pharmaceutical Excipient Council of the Americas[14]. In addition, the Elemental Impurities Pharma Consortium has published a commercial database comprising analytical data on elemental impurities from over 100 different materials, including pharmaceutical excipients, and dyes, etc.[15].

Risk assessment frequency

A full risk assessment will need to have been completed as part of the regulatory submission for a new product filing and appropriate actions taken ready for manufacture. Once a product is approved then the manufacturer will need to update the risk assessment whenever changes are made to the process – for example, when a packaging change is made, or a new raw material supplier is introduced to the supply chain. The updated risk assessment may require the introduction of additional testing or could justify reduction of testing. In the new risk assessment, any actions should be submitted as part of the annual report to the FDA as per the Chemistry Manufacturing and Controls (CMC) Guidance for Industry[16].

Part 2: So, what does a 'heavy metal contaminants in cannabis' risk assessment approach look like?

It's difficult to fully comprehend how the cannabis industry can implement a comprehensive risk analysis strategy for elemental contaminants in consumer and medicinal products in a similar way to what the pharmaceutical industry began in the mid-1990s. Pharma realized that the compendial methodology (sulfide precipitation visual observation) was inadequate to protect public health and in an effort to maintain global harmonization on this initiative joined in and expanded upon the United States Pharmacopeia's (USP's) update process with the initiation of the ICH Q3D initiative. There is very little incentive for the cannabis industry to do this at this present time. Since there is no national regulatory body driving uniformity or regulation, the industry is basically regulating itself with some oversight from the individual state regulators.

Most states regulate the big four heavy metals, but there is evidence in the public domain that at least another ten are worthy of consideration. It's likely that the momentum for change will come from consumers and consumer advocates and the desire to have safer products. Product recalls and certificates of analysis (COAs) that are vague and, in some cases, intentionally falsified will in the long run likely drive the need for a unified approach with consequences for noncompliance. However, there could be a better way to scrutinize the different aspects of cannabis manufacturing through a root cause analysis process similar to the fishbone approach used by the pharmaceutical industry. But who would be responsible for driving it is uncertain at the moment? The global pharmaceutical industry had the International Council for Harmonization of Technical Requirements for Pharmaceuticals (ICH) to carry out the risk assessment study, but no such regulatory bodies exist in the cannabis industry. So, it would have to be determined what standards organizations and interested stakeholders outside the federal government would be willing to take on this responsibility. In the meantime, it is important to have a basic understanding of how the problem could be approached!

Breakdown of the cannabis production process

In parallel with the fishbone diagram shown in Figure 1 we can identify six different processes in the production of cannabinoids that can lead to the introduction of elemental impurities in the final product:

- Cultivation and growing of cannabis and hemp.
- Extraction and purification of cannabinoids.
- Processing of specific cannabis/hemp consumer products.
- Manufacturing of infused products.
- Product packaging.
- Consumer delivery.

These could be represented by a modified fishbone approach shown in Figure 2, by using many of the guidelines and suggestions enummerated in the pharmaceutical version.

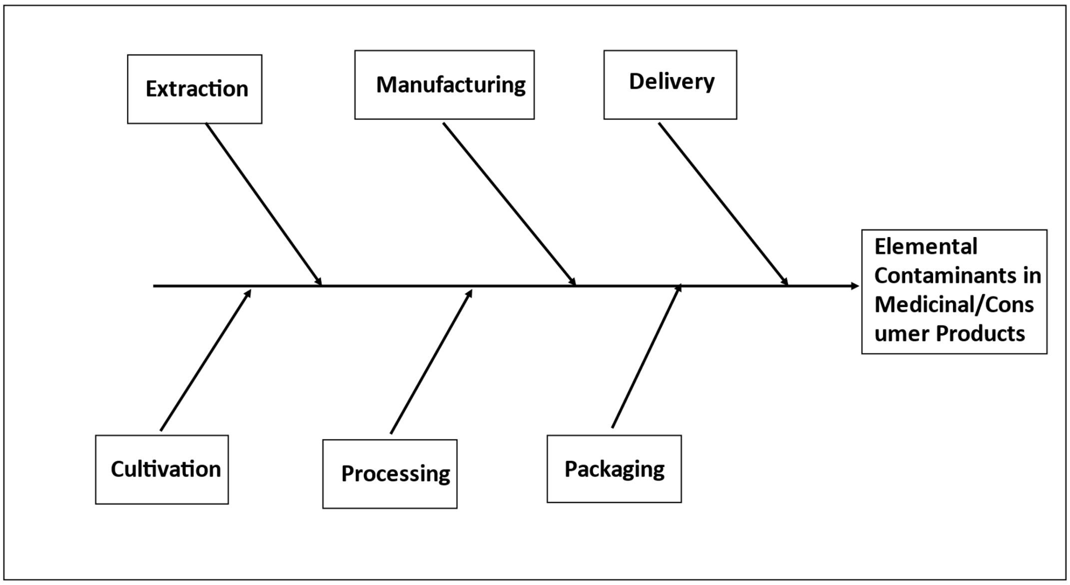

Figure 2: Possible Fishbone approach for the cannabis industry.

Let's take a closer look at each of these processes, particularly how they can impact elemental contaminants in the final medicinal/consumer products and recommendations on how to reduce them.

Potential sources of heavy metals

Considerations about where to grow cannabis and hemp are going to be critically important because it could have serious implications on the level of heavy metals that are absorbed by the plant and its resulting safety for human consumption of cannabinoids. Historically, apart from the western and southern regions of the US, much of the cannabis in the US has been grown indoors in greenhouses under controlled growing environments, so the absorption of heavy metals into the plant has been kept in check reasonably well.

But in 2020 it became legal to grow hemp for CBD production anywhere in the US. As a result, it became more challenging to keep the levels low, because most of the hemp plants are grown outdoors on farms where the soil might be an additional source of contamination[17].

So, let's first look at potential sources of elemental contaminants in cannabis and hemp from a growing and cultivation perspective and then we'll focus on the impact of the extraction, processing, production, and packaging and delivery processes.

Part 3: The extraction of cannabinoids

Cultivation and growing sources

Plant-based phytoremediation is emerging as a cost-effective technology to concentrate and remove elements, compounds, and pollutants from the environment[18]. And within this field, 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 land remediation methods[19]. However, the natural inclination of these plants to absorb heavy metals from the soil could potentially limits its commercial use for the production of medicinal cannabinoid-based compounds. A number of studies provide convincing evidence that cannabis is an active accumulator of heavy metals such as lead, cadmium, arsenic, mercury, magnesium, copper, chromium, nickel, manganese, and cobalt[20, 21, 22, 23].

Main factors for metal uptake

The health and growth of all plants rely on essential nutrients and minerals being available in dissolved, ionic forms in the soil. To maintain enough water to survive and thrive, the plant's primary means of facilitating the movement of water is through transpiration, which is a highly efficient means of drawing a concentrated solution of minerals and nutrients out of the soil. Transpiration works by the evaporative loss of water from the shoots, which is controlled by the opening and closing of specialized pores (known as stomata) embedded in the surface of the leaves that initiate gas exchange. When the stomata are open, the pressure potential of the plant becomes very negative, creating a vacuum effect that draws water and nutrients into the plant, moving it from the roots to the shoots. Unfortunately, this is also the mechanism that the plant draws in heavy metal contaminants in addition to the nutrients.

The rhizosphere is the region of soil in the vicinity of plant roots. Its chemistry and microbiology are influenced by the roots' growth, respiration, and nutrient exchange[24]. Unfortunately, under certain conditions, the plant's root system will preferentially absorb heavy metals over other minerals, which cannot be explained exclusively by passive ion uptake. The hyper-accumulating properties of cannabis and hemp aren't fully understood, but are partially dependent upon many different factors, including soil pH, availability of other metal/mineral ions in solution, the nitrogen/phosphorus/potassium (NPK) ratio and the ability of the plant's natural metalloproteins, which act as chelating compounds to bind with the heavy metals to reduce the rate of absorption and overcome their toxic effects.

It should also be noted that the plant's natural polyamine compounds will strengthen the defense response of plants and enhance their defense against diverse environmental stressors, including toxicity and oxidative stress. Gwen Bode wrote an excellent article on the underlying mechanisms of heavy metal uptake by cannabis plants, which should be essential reading for any cannabis grower[25].

Based on evidence in the public domain, there are approximately 15-20 heavy metals found in polluted ecosystems that could be potential sources of contaminants, including lead, arsenic, mercury, cadmium, nickel, vanadium, cobalt, copper, selenium, boron, thallium, barium, antimony, silver, gold, zinc, tin, manganese, molybdenum, tungsten, iron, and uranium. Many of these elements exist as different species or metalloids, based on their oxidation state, organic/inorganic/ionic form[26], or as engineered nanoparticles that could find their way into wastewater streams[27]. Their levels of toxicity would need to be investigated further, but there is a compelling case to be made that the many of these elements, metalloids, and speciated forms could be the future basis of a federally regulated panel of metal-based contaminants in cannabis and hemp.

Outdoor growing sources

Image credit: Glenna Thomas.

Let's take a closer look at some of the "real-world" sources of elemental contaminants that are supported by evidence in the public domain. It's only when cannabis and hemp cultivators and growers have a good understanding of this problem can they hope to reduce or even eliminate them. This isn't an exhaustive list, but it offers some suggestions and a good starting point to begin investigating them:

- Water is a critically important nutrient for cannabis plants. Ensure that only the highest quality water is used and test on a regular basis for common pollutants. Refer to ICH Q3D guidelines for water quality used in pharmaceutical manufacturing[7].

- When grown outdoors, if possible, the soil chemistry should be characterized to make sure that the elemental contaminants are at acceptable levels. In particular, the acidity (pH) of the soil should be optimized to minimize the amount of heavy metal ions in solution. Explore the use of natural chelating agent, such as humic acid or a soil amendment medium like biochars (any biomass heated in an oxygen-lean atmosphere), to bind with the harmful metallic contaminants to minimize their uptake by the plant's root system[29].

- In areas where gold and silver mines are found, there is the potential for high mercury levels in the soil, as mercury amalgamation is a well-accepted extraction method. These mines are particularly prevalent in the growing states of California, Oregon, and Washington, which have some of the highest density of outdoor cannabis farms in the US[30, 31].

- Metal smelting plants will experience heavy metal contamination in surrounding areas. Lead and copper ores in particular contain high levels of arsenic[32].

- Environmental Protection Agency (EPA) superfund sites, especially those involved in the manufacture of weapons, could have high levels of radionuclides such as uranium in the soil and the groundwater[33].

- Fly ash waste from coal-fired power plants is extremely high in heavy metals from the coal combustion process. Surrounding areas where the fly ash has been dumped into ponds will likely seep out and contaminate the soil and ground water[34].

- Decades of leaded gasoline usage has contaminated much of the soil close to and around major highways and roads[35].

- Many industries are known to emit elemental mercury into the atmosphere, including coal-fired power plants, metal refineries/smelters, petrochemical plants, and cement works. It's well documented by the Clean Air Act that up to 100 tons of mercury are emitted by US industries annually, much of it being converted into the highly toxic methyl mercury by aquatic species by the process of bioaccumulation[36].

- Avoid planting hemp in fields that were once apple orchards. Spraying apple trees with fungicides containing lead arsenate was a common practice, so it is inevitable high levels of arsenic and lead will have polluted the soil[37, 38].

- Wood preservation chemicals contain high levels of copper, arsenic, and chromium. Areas around these plants are likely contaminated[39].

- Low-grade fertilizers/nutrients made from phosphate rocks contain significant amounts of elemental impurities[40].

- Nickel has been promoted as a cannabis flower/bud-enhancer and silicon as a way of increasing shoot size, which means that higher levels of nickel and silicon will invariably end up in the cannabis product. These elements are typically not required by the vast majority of states, so they would escape the scrutiny of most state regulators[41, 42, 43].

- Some glyphosate-based herbicides are rich in heavy metals[44].

- Although there is no speciation requirement in the current state-based limits for heavy metals, both dietary supplement and pharmaceutical regulators have shown that inorganic and organic forms of arsenic and mercury should be monitored if the maximum limits for the total amount of the element is exceeded. In addition, depending on where the cannabis/hemp plants are grown, the location will also dictate whether other speciated forms should be monitored. Examples of this might include the highly toxic hexavalent chromium (CrVI) compared to the relatively innocuous trivalent species (CrIII)[45].

- At some point in the future, nanoparticle characterization in the soil and uptake by the cannabis plant may be required, particularly when there are regulated methods for environmental and food-based nanoparticle assays[27].

Indoor growing sources

Although an indoor growing environment is far more controlled than cultivating plants outdoors, there are still many opportunities for picking up elemental contaminants. Nutrients, fertilizers, and potable water are three of the potential sources of metal contamination. As a result, indoors plants cultivated in a synthetic soil, grow bags, Rockwool medium, or hydroponically grown are highly dependent on the nutrients, minerals, and water used. For that reason, high quality fertilizers and a source of clean water are essential for healthy plants. Here are three potential areas of concern when growing plants indoors.

- Last year the EPA estimated that 30 million people in the US live in areas where drinking water violated safety standards. The EPA defines a list of primary and secondary elemental maximum contaminants levels (MCLs) in drinking water and overseas all local water authorities and municipalities in the US to ensure compliance. It's important to know these levels in your region to make sure they are well below the limits for metal impurities (they will be posted online by your local water authority). Also keep in mind that these are levels for samples taken at the water treatment plant and not the levels measured at your home or growing site. EPA mandates that a municipality only has to measure water quality at its customers' sites every two years and has to take remedial action only if ten percent of those sampled are above the MCL. A recent example of what can go wrong is provided by the lead-contaminated drinking water in Flint, Michigan. The source was changed from lake water (Lake Huron) to the local Flint River without understanding the chemistry and its corrosion properties. As a result, the water partially dissolved the inside of the old lead pipes and ended up contaminating the drinking water supply[46, 47].

- Decades of using lead-based pigments in residential and commercial paint has meant that many of the older homes and buildings still contain these types of paints, which have often been painted over, but still produce dust/particles that can potentially be problematic[48].

- Some plasterboard used in the construction industry is made from gypsum-based flue gas desulfurization (FGD) waste products mixed with a silicate material known as clinker. FGD is produced by scrubbing particulate emissions from coal-fired power plants, which are notoriously high in heavy metals[49].

Cannabis extraction

Extraction is necessary to purify and concentrate the essential cannabinoid compounds from the plant while also removing the undesired contaminants. These compounds are mainly contained in the female flower's trichomes, small glandular hairs protruding from the surface of the plant that secrete a sticky resin that contains most of the cannabinoids and terpenoids of interest. When the optimum extraction method is employed, it can either result in pure, isolated compounds or more natural, full spectrum extracts containing a wide array of the cannabinoids and terpenoids found in the source material. Most consumers of cannabis are familiar with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), but these are only two of the 100-plus cannabinoid compounds found in cannabis.

The ability to extract the desired compounds allows medicinal products to be manufactured based on the desired therapeutic effect for the specific ailment or disease being treated. However, cannabis also contains 140-plus different terpenes (terpenoids), aromatic compounds best-known for giving cannabis its distinctive fragrances and flavors. Terpenes are currently gaining a great deal of attention, not only for their potential therapeutic value, but also because of the so called "entourage effect" when combined with other cannabinoids. The technology needed to extract bioactive compounds from the flower's trichomes or other parts of the plant clearly depends on medicinal product goals. It is also important to emphasize that when cannabis is harvested, it contains practically no THC and CBD. There are, however, significant amounts of tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA). So, to convert THCA and CBDA to THC and CBD, the cannabis must first be heated to remove the carboxyl functional group (COOH) from the respective THCA and CBDA molecules. This process, known as decarboxylation, converts the compounds into THC and CBD, respectively. These chemical structures are the gateway molecules to the human endocannabinoid system (ECS) that runs throughout the central nervous system, delivering the desired therapeutic/psychoactive effect. It is therefore clear that heat is a very efficient way to increase the bioavailability of certain compounds in cannabis. However, heat alone does not give us the ability to select which compounds we want to activate. This is achieved by carrying out extraction procedures using different organic solvents, often combined with a precise control of temperature, pressure and flow, which allows for the optimization and fine-tuning of the products being made.

Note: Although not the focus of this article, delta-8-THC is another compound of concern. It is manufactured synthetically from CBD[50] and has only recently entered the marketplace. The potential for elevated levels of contaminants is much higher than with delta-9-THC or CBD because of the manufacturing process, which uses solvents such as toluene and sulfonic acid as a catalyst. This results in an impure product that requires further clean-up to purify, which often does not happen because of the higher cost of production.

Extraction approaches

Image credit: Glenna Thomas.

The methods used to extract cannabinoids are as varied as the compounds themselves. Some techniques use temperature, pressure, and flow, relying on thermal and mechanical forces to remove valuable compounds from the plant's trichomes. Others rely on organic solvents to carry the desired compounds into another solution, which is then processed again to remove the solvent. Some even use microwave- and ultrasonic-assisted extraction methods. Whatever extraction technique is employed, they all use a combination of solvent, temperature, pressure, and time in a precise, controlled manner to access one or many of the cannabinoids, flavonoids and terpenes present in the cannabis plant. There are a multitude of different extraction techniques, all with their own strength and weaknesses. Let us take a closer look at three of the most common approaches[51].

Alcohol extraction:

Alcohol extraction is one of the most efficient extraction methods for processing large batches of cannabis flower, and can be done in hot, cold or room temperature conditions. Typically carried out using hot ethanol (or propanol), extraction is generally accomplished using the Soxhlet extraction technique, which cycles the hot solvent through the solid cannabis flower, stripping the cannabinoids and terpenes from the flower in the process. However, the method can be difficult to scale up to large batches. The process also often extracts unwanted chlorophyll and plant waxes from the cannabis flower due to the polarity of the ethanol solvent. The mixture then requires several additional postprocessing steps (filtering, distillation, evaporation, etc.). Cold ethanol or even room temperature helps to avoid this problem, as the cooler temperatures make it a little more difficult for the unwanted polar plant waxes and chlorophylls to dissolve in a polar alcohol solvent.

Hydrocarbon extraction:

Hydrocarbon extraction, normally achieved using butane or propane, is able to extract a greater variety of terpenes from the cannabis material than the ethanol extraction method. For products such as vape oils or oral tinctures, where the cannabis extract is unlikely to be masked by other flavors, preserving these terpenes help to give the extract a specific flavor and aroma. This improved extraction comes as a result of the low boiling point of the hydrocarbon (butane, -0.5°C) at standard pressure. After cold butane solvent has washed over the cannabis plant material and extracted its oils, the solvent can be easily cold-boiled off to leave oil that is more representative of the entire plant as more of the temperature-sensitive terpenes will be retained. However, like the ethanol method, hydrocarbon extraction cannot be so easily scaled up to deal with large single batches of cannabis material. While the low boiling point of butane is advantageous when the solvent needs to be removed without removing any other organic compounds, these flammable solvents can also potentially present a safety hazard to workers. Hydrocarbon extraction is a very hands-on process and not easily automated, meaning that there is almost always an operator in close proximity to the extraction vessel. In the interest of safety, hydrocarbon extraction is typically done on a much smaller scale, though the speed and efficiency of this extraction method means its overall output still makes it suitable for large-scale operations.

Super/subcritical CO_2 fluid extraction:

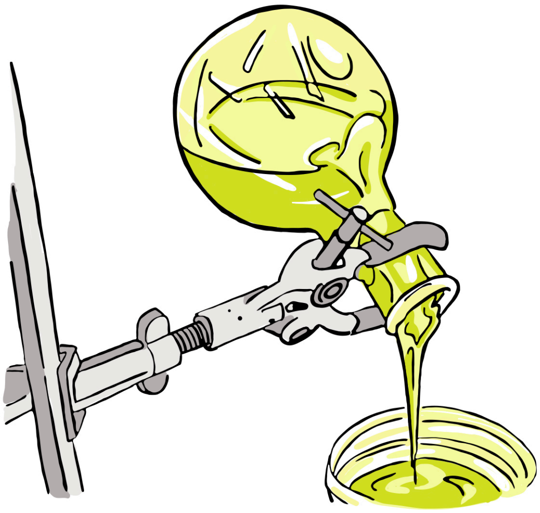

Image credit: Glenna Thomas.

Super- or sub-critical CO_2 fluid extraction is relatively new to the cannabis industry, but it is already becoming a popular choice. In brief, the method involves using special pressure, temperature, and flow control equipment to turn gaseous CO_2 into a super or sub-critical nonpolar fluid. When passed over cannabis material, the fluid can easily extract plant waxes and oils from the cannabis. Super-critical fluid extraction employs higher temperature, pressure, and flow, which is good for THC/CBD yield, but tends to extract more of the non-targeted compounds including contaminants. The subcritical method employs a much lower temperature, pressure, and flow, which sacrifices yields, but leaves many of the contaminants behind. When cannabis is processed under relatively low pressure, temperature and flow conditions over a longer time, the amount of post-processing that is required after extraction is minimized and can usually be used without any further processing. When using this type of extraction, winterization is often used to clean up the extract and remove unwanted waxes and fatty acids. This is achieved by soaking the extract in cold ethanol (-20°C) for approximately 24 hours and then filtering out the unwanted solid waxes and lipids. The major downside of CO_2 extraction is the high initial equipment cost, which can be prohibitive for start-ups or small businesses. However, unlike ethanol or butane, CO_2 is a very flexible and tunable solvent and can pull unique compounds from botanicals using different pressures, temperatures, and flows. In addition, the gas is far safer than the flammable hydrocarbon methods. It is also worth noting that butane extraction often results in a more concentrated product, which can be detrimental if the cannabis material contains toxins or contaminants from the cultivation process.

Extraction objectives

The optimum extraction method is often selected based on what cannabinoid/terpenoid combination is required, which is typically chosen based on the required medicinal product or desired therapeutic or psychoactive outcome. In other words, a processor does not decide on whether they are going to use CO_2, butane, ethanol, or another extraction process. Instead, their decision is driven by what isolate/concentrate they are trying to make, based on the desired finished product. Whether it is a vape pen, a gummy, a cookie, a tincture, or an oil, it begins with the final product and then it is "reverse engineered" to get the ingredients for those products. There is then a final selection of the extraction method that will best provide those ingredients.

This fundamental "reverse engineering" principle can even be related back to the cultivar, as it is important to select the plant that will provide the desired molecular profile or to manipulate the chemistry to get the desired ingredients. David Hodes wrote an excellent review of the major commercial extraction methods and the pros and cons of using each approach, which is highly recommended reading for any current or new processor who wants to optimize their extraction procedures[52].

Production of cannabis consumer products

So, with this as background information, here are some suggestions to reduce the likelihood of metals contaminating the cannabinoids during the cannabis preparation, extraction, and purification process:

- Minimize the use of metal-based processing/extraction/blending equipment. Perhaps there is a polymer alternative that could be used? In particular, avoid the use of stainless-steel mixing vats, processing vessels, cutting blades, scissors and grinding equipment. Depending on the quality/specification of the stainless steel, metals ions could find their way into the processed cannabis flowers and eventually into the extracted oils and concentrates[53].

- If possible, use an optimized solvent and extraction/distillation process to minimize the amount and number of metals ending up in the extracted products. It would also be useful to characterize the metal content at every step of the manufacturing process from the extraction and purification to the final consumer product[54].

- Some extraction processes are known to be better for low carry-over of metals. For example, a patent application by GW Pharmaceuticals (manufacturer of Epidiolex for childhood seizures) in 2008 for the extraction of pharmaceutically active components from plant materials showed the benefits of a sub-critical, low pressure/low temperature/low flow fluid extraction process using carbon dioxide to minimize the carryover of metals into the cannabinoid extracts[55]. Use ultra-clean solvents and chemicals low in heavy metals for the extraction, distillation, concentration, and infusion of cannabinoids from the plants[56].

- Make sure the source of water used in the cannabis production process is contamination-free. Minerals or elemental impurities in the water supply should be below the Environmental Protection Agency (EPA) maximum contaminant levels (MCL), otherwise the extracted material could pick up metals from the water. A contaminated water supply could be a real concern with older buildings that potentially have lead pipes or copper/iron pipes connected with lead-based solder. If in doubt, use pharmaceutical-grade water as per ICH Q3D guidelines[7, 58, 59].

The balance between low heavy metals or high potency yield

It is well-recognized that many metal ions and species are only slightly soluble in organic solvents, but this is dependent on a combination of the specific metal ion, its species and oxidation state, the polarity and boiling point of the solvent and the extraction temperature and pressure used. This begs the question, what is the optimum extraction technique to minimize the heavy metals carried over but to maximize the cannabinoid yield?

It is well-accepted that most cannabinoids are not very water-soluble, so what is the right balance with regard to solvent choice and polarity to optimize this extraction process. Unfortunately, there is very little information in the public domain on this topic. We thought there might be a comparison between heavy metal levels in cannabis flowers and the resulting extracted concentrate but there does not seem to be any published literature on this topic, indicating that if it has been studied, the information remains proprietary. As a general rule, it appears that everything is geared towards maximum potency yield, and much of the literature just assumes that most of the heavy metals are left behind in the extraction/distillation process and are not being co-extracted/co-distilled with the cannabinoid.

This is probably a sound strategy if the plants have been cultivated indoors, where the growing conditions are far more controlled and the heavy metals in the plant should be relatively low. However, that is not always the case. For example, some indoor growers are now using organic fish emulsion/

hydrolysates, which are notorious for containing high levels of mercury[60]. This is predominantly a result of bioaccumulation up the food chain from the smaller bottom feeders to the large predatory fish. The mercury is typically environmental fallout from industrial activity (power plants, metal refineries etc.), which ends up in the sediment of ponds, rivers and lakes and often gets converted to methyl mercury (CH_3Hg), which is even more toxic than the elemental form[61]. We are also now beginning to see more CBD products derived from hemp in the marketplace, which is predominantly grown outdoors, where the cultivation conditions and, in particular, the quality of the fertilizers are far less controlled[62]. This leads to the conclusion that heavy metals in plants grown outdoors are potentially going to be much higher. For these reasons, there clearly needs to be a scientifically driven investigation to better understand the level of heavy metal movement from the plant through each step of the preparation/extraction/distillation/concentration process. I am very hopeful that a concerned processor, university, or research organization will take up this challenge.

Part 4: Production, packaging, and delivery of cannabis consumer products

Manufacture of cannabis products

Once the cannabinoid product has been manufactured, serious consideration must be given to the selection and composition of diluent mineral oils, flavoring compounds, and recipe ingredients. For example, raw materials such as fillers, excipients, dissolution compounds – which are added to these products – could possibly be contaminated with heavy metals. For that reason, it is critically important to carry out quality control testing of all components. Even if there are no heavy metals in the cannabinoid extract, it could exceed the regulated limits because of contaminated additives or ingredients. In fact, a recent study by researchers at the University of Illinois showed that cacao beans grown in certain countries in Latin America contained abnormally high levels of cadmium. Chocolate made from these beans could easily end up in cannabis consumer products such as brownies or chocolate chip cookies[63]. It is also worth emphasizing that many cannabinoid products (in particular CBD derived from hemp) are being sold and labelled as dietary supplements, which is attracting the attention of federal regulators, because it violates the Federal Dietary Supplement Health and Education Act (DSHEA) and could potentially put the health and safety of consumers at risk.

Image credit: Glenna Thomas.

Packaging, storage and container systems

It is also important to characterize the material used for packaging the products, particularly if they are in liquid form. This was a major consideration when the pharmaceutical industry was carrying outs its risk assessment study, because drug products are often stored for long periods of time, which could potentially allow them to degrade or become contaminated from the packing material. For example, some low-quality borosilicate glasses and inexpensive plastic containers are notorious for metallic contamination, which could leach out into the product during storage. In fact, researchers at the Florida Department of Agriculture found abnormally high levels of lead in CBD extracts, which had been

leaching out over time, and was most likely coming from the lead-based ink used in the graduated dropper bottles. One sample resulted in lead levels 36 times higher than the state's maximum action limit of 0.5 parts per million (ppm)[64]. In addition, a recent study presented at a cannabis science conference showed that rolling papers contained abnormally high levels of lead[65].

Delivery devices

It is worth pointing out that, historically, most consumers of recreational cannabis have delivered their cannabinoids via the smoking route. Smoke chemistry has been predominantly investigated in tobacco products, but many studies over the past ten years have highlighted the qualitatively similar carcinogenic chemicals contained within both tobacco and cannabis smoke[66, 67].

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[68]. Quantitatively, there were lower heavy metal concentrations in cannabis smoke condensates, mainly because the cannabis supply was grown hydroponically. In addition, the soilless 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 present in the growing cycle of the cannabis, it was the liquid nutrients and fertilizers used in the hydroponic systems that contributed most to the heavy metals. There is a great deal of information in the public domain about heavy metals in tobacco and tobacco products, such as nicotine and electronic nicotine delivery (END) devices[69, 70].

Vaping systems

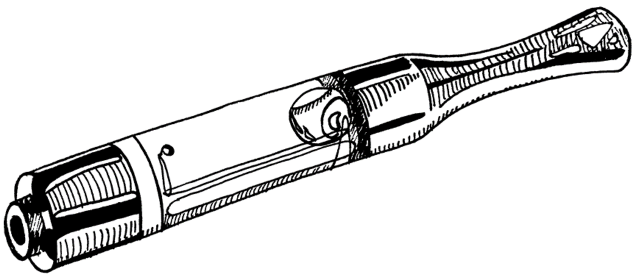

Image credit: Glenna Thomas.

However, the more common way of inhaling cannabis products today is via vaping sticks, carts, or pens. The demand for these vaping devices is growing so fast that they are very loosely regulated, which is attracting manufacturers with very little regard for safety. There are literally millions of these devices out in the marketplace where the cannabis flower, extract or oil is heated up to about 200-300 °C and the aerosol is vaporized into the consumer's mouth.

The problem with this mode of delivery is that many of the components inside these vaping devices are metal, including the tank, coil, mouthpiece, and battery terminals, which are typically made from materials such as stainless steel (iron, chromium, nickel, cobalt), brass (copper, zinc, lead), chromel (chromium, nickel), inconel (nickel, chromium, and iron), Nichrome (nickel, chromium) and soldered battery connectors (lead, antimony, tin). At these kinds of temperatures, dissolved metals or even fine metallic particles can easily be delivered to the consumer's air pathways and lungs via the mouth[71].

Unfortunately, there is no standardized test for these elemental contaminants in the vaped aerosol, so even though the cannabis flower, oil or extract in the tank might contain elemental impurity levels below the regulated limits, the vaping mechanism is generating an entirely new panel of pollutants, which is escaping the scrutiny of state regulators[72]. The list above demonstrates that most of the metals under discussion here have much higher toxicity (e.g., lower permitted daily exposure) when inhaled compared to being consumed orally.

This is of great concern, because unlike oral delivery through the gastro-intestinal digestion system, the lungs and respiratory system were designed to allow us to breathe. They bring oxygen from the air into our bodies and send carbon dioxide out. Air enters the respiratory system through the nose or the mouth. If it goes in through the nostrils there are tiny hairs called cilia that protect the nasal passageways and other parts of the respiratory tract, filtering out dust and other particles that enter the nose. There is no such filtering system in the mouth, so if any metal particulates make it into the aerosol there is no mechanism to stop them entering through the respiratory system into the lungs, where they can do serious damage, particularly if vaping is carried out on a regular basis over extended periods of time. This fact makes it critically important to characterize the metal contaminants in the aerosol, not just in the tank. Unfortunately, this is not straight forward because the vaping aerosol condensate, which is a mixture of hydrophobic and hydrophilic liquids must be trapped and collected before it gets introduced into the ICP-mass spectrometer for quantitation. This involves using a modified smoking machine, which can mimic the inhalation profile of a typical cannabis vaping consumer, which is very different to someone who uses a nicotine vaping system. The bottom line is that it requires specialized equipment and a person with a high level of knowledge and experience in working in the ultra-trace element environment[73]. In 2019 a nationwide outbreak of e-cigarette and vaping use-associated lung injuries (EVALI) led to 3000 people developing pneumonia-type symptoms and 68 deaths, mainly from illicit THC vaping devices containing vitamin E acetate[74]. As most state-based regulations only specify lead, arsenic, cadmium, and mercury they would fail to identify the other elements if they were present in the vaping aerosol because there is no requirement to test for them in most states. The last thing the industry wants is for another EVALI-type crisis by not paying enough attention to these additional elemental contaminants.

Note: Smoking cannabis using water pipes (bongs) is another way of delivering cannabinoids to consumers, but they are beyond the scope of this white paper. However, it should be noted that most of these devices are typically made from low quality materials like borosilicate glass, ceramic or plastic which often have metallic impurities associated with them and could potentially leach out of the material over extended periods of use.

Final thoughts

It took the pharmaceutical industry over 20 years to fully-understand all the sources of elemental impurities in the manufacture of drug products. The sector finally accomplished this by classifying the impurities' toxicity impact and the risks of finding these impurities throughout the entire manufacturing process. It is clear that the cannabis industry has a great deal to learn about this process. The way to minimize heavy metals in cannabis and cannabis products is to first understand and characterize the cultivation process. Unfortunately, this is often very challenging, particularly if the plants are being grown outdoors. However, by carefully selecting the right cultivars, understanding the soil chemistry and the use of high purity fertilizers, nutrients, and water, the industry can minimize the plants' uptake of elemental contaminants. Moreover, by optimizing the extraction and purification method, processors have the ability to reduce levels of heavy metals in the final cannabinoid extracts. Very often there are many choices when selecting an extraction technology, depending on the desired extract or the products being made for a therapeutic outcome. It is clear that elemental contaminants can be minimized by optimizing the entire production process, including extraction solvent, temperature/pressure/flow conditions, and the other purification techniques, including evaporation, distillation, and filtration. However, this must also be extended to include the packaging and delivery systems, which are all important areas to characterize in order to ensure that cannabis consumer products are free of heavy metals and safe for human consumption.

A final word of caution! The insatiable consumer appetite for cannabis products in the US is being fulfilled from outside the country. Yunnan Province in southern China is now producing CBD-products for the US market[75]. This should not be surprising, considering the US industry cannot produce enough to supply the huge demand. What is more disturbing is that the metal refining for the electronics industry in China has produced some of the most contaminated waste sites in the world[76].

Experience has cautioned us that consumer products coming from China are not always of the highest quality. So, it is imperative that no matter where the products are sourced, especially if it is from outside the US, testing the hemp and CBD products for a comprehensive suite of elemental contaminants is critically important. Our appetite for the cannabis and hemp plant and their medicinal and recreational properties is unlikely to diminish in the near future, so we are going to have to balance that with its natural instinct to absorb heavy metal from its growing medium. Hopefully we will not be tempted to sacrifice one for the other and jeopardize consumer safety!

Following the direction of the pharmaceutical industry and implementing a comprehensive risk assessment study is one way of minimizing these risks. It remains to be seen whether this approach will be taken up by individual manufacturers, driven by state regulations, or perhaps even addressed nationally as was done with USP 232 and ICH Q3D and driven through a regulatory/industry consortium established with the goal of providing minimum national standards for cannabis products in any of their forms. Federal scrutiny will clearly impact this decision, but it will be interesting to see how quickly this happens. Only time will tell!

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