CANNABIS PATIENT ADVOCACY ASSOCIATION

March 5, 2020

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RE: SB821

The Cannabis Patient Advocacy Association requests that either the proposed Maryland Code, Agriculture § 5-105, as contained within SB821, be stricken in its entirety or, in the alternative, that it be amended to include the following language:

A GROWER MAY NOT USE A PESTICIDE OR HERBICIDE TO GROW MEDICAL CANNABIS THAT WILL OR MAY BE BURNED AND INHALED BY THE QUALIFYING PATIENT, INCLUDING BY SMOKING OR USING AN ELECTRONIC DEVICE TO DELIVER CANNABIS OIL.

THE MEDICAL CANNABIS COMMISSION MUST ADOPT REGULATIONS REQUIRING AFFIXATION OF A LABEL ON ANY MEDICAL CANNABIS PROVIDED FOR SALE TO QUALIFYING PATIENTS WHICH SHALL CONTAIN HEALTH AND SAFETY INFORMATION, PLACED IN A CONSPICUOUS MANNER, INCLUDING INFORMATION ON:

> **ANY PESTICIDE OR HERBICIDE USED TO GROW THE MEDICAL CANNABIS;**

> **ANY ADDITIVES TO THE MEDICAL CANNABIS;**

> **ANY OTHER INFORMATION ABOUT POTENTIAL HEALTH OR SAFETY RISKS RELATED TO THE USE OF THE AFOREMENTIONED PESTICIDES OR HERBICIDES**

Marylanders using medical cannabis cannot be put at risk of harm from pesticides on their medication. While Maryland Code, Agriculture § 5-105(h) requires compliance with federal laws in this area, even the United States Environmental Protection Agency (EPA) standards for pesticide use in food products may not be adequate to properly ensure Maryland's most medically vulnerable patients are safe from pesticide harm. Pursuant to Maryland Code, Agriculture § 5-101(t), " 'Pesticide' means (1) any substance or mixture of substances

intended for preventing, destroying, repelling, or mitigating any insects, rodents, fungi, weeds, or other forms of plant or animal life or viruses, except viruses on or in living humans or other animals, which the Secretary declares to be a pest; and (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant." The EPA's process for setting tolerance is pesticide and food product specific. "In setting the tolerance, EPA must make a safety finding that the pesticide can be used with 'reasonable certainty of no harm.' To make this finding, EPA considers the toxicity of the pesticide and its breakdown products, how much of the pesticide is applied and how often, and how much of the pesticide (i.e., the residue) remains in or on food by the time it is marketed. EPA ensures that the tolerance selected will be safe."[1] There is no accurate way to assess the cannabis plant at this time.

Additionally, the EPA only reevaluates the data and safety of a pesticide every 15 years post-registration.[2] Between 2009 and 2013 alone, the EPA took at least ten actions to cancel the use of specific pesticides previously deemed safe for human consumption at acceptable levels.[3] Moreover, the EPA sets levels for products consumed by ingestion not combustion thereby leaving a gap as to what is safe for medical cannabis flower and products consumed by combustion. A 2013 study found that pesticide residues on the original cannabis plant "will directly transfer into the mainstream smoke and ultimately the end user" with rates as high as 69.5% when smoked without a cotton filter.[4]

Though healthy adult humans may not suffer from harmful effects from low level, short-term exposure to pesticides,[5] children are naturally at a greater risk of harm from pesticides due to the developing nature of their organs as well as their immune, metabolic and enzymatic systems.[6] Sick children are especially vulnerable as are the geriatric, immune-compromised and chronically ill because pesticides can structurally and

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[1] United States Environmental Protection Agency: Food and Pesticides as accessed at (https://www.epa.gov/safepestcontrol/food-and-pesticides).

[2] United States Environmental Protection Agency: Food and Pesticides as accessed at (https://www.epa.gov/safepestcontrol/food-and-pesticides).

[3] United States Environmental Protection Agency: Food and Pesticides as accessed at (https://www.epa.gov/safepestcontrol/food-and-pesticides).

[4] Sullivan, N., Elzinga, S., and Raber, J. Determination of Pesticide Residues in Cannabis Smoke. *J. of Toxicology.* 2013: 1-6 (2013). (copy attached: Appendix A)

[5] Occupational and environmental exposure to pesticides and cytokine pathways in chronic diseases (Review), Gangemi, S., et al., Int J Mol Med. 38(4): 1012-1020 (2016).

[6] United States Environmental Protection Agency: Children Are at Greater Risks from Pesticide Exposure (2002) as accessed at https://archive.epa.gov/pesticides/regulating/laws/fqpa/web/html/kidpesticide.html.

functionally alter the immune system.[7] A review of the literature shows that even at low doses, chronic exposure to pesticides is associated with increased risk of cancers as data shows an immunotoxic effect on the immune system's ability to recognize and control tumor growth.[8] For many medical cannabis patients, daily consumption of their medication keeps them healthy and well. Even at low, acceptable levels, chronic exposure to pesticides could cause medical cannabis patients a reasonable certainty of harm.

The State of Maryland currently lists over 100 acceptable pesticides[9] for application to medical cannabis cultivated for use by qualifying patients. Each Department of Agriculture listing appears to be a specific commercial product. Qualifying patients or their caregivers must access the Safety Data Sheet (SDS) of each commercial pesticide product and decipher the scientific data themselves to determine whether the product is actually safe for their medical use.[10] Safety Data Sheets are often hidden on the product's website, and difficult to understand without scientific background. More importantly, qualifying patients and caregivers cannot access the SDS information they need to consider in their medication purchases because pesticides are not currently listed or labeled on medical cannabis products grown, processed, manufactured and dispensed to qualifying patients and caregivers in the State of Maryland. In fact, an informal review of qualifying patients' purchased products found that very few explicitly stated that no pesticides were used in the product. Between December 2018 and December 2019, thirty-five thousand, nine hundred and ninety-eight (35,998) pounds of medical cannabis flower was purchased by qualifying patients and caregivers.[11] One study found that when smoking cannabis without a cotton filter, users may be exposed to up to 69.5% of the pesticide residues from the original plant.[12] While THC may have protective properties against the harmful

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[7] Occupational and environmental exposure to pesticides and cytokine pathways in chronic diseases (Review), Gangemi, S., et al., Int J Mol Med. 38(4): 1012–1020 (2016).

[8] Occupational and environmental exposure to pesticides and cytokine pathways in chronic diseases (Review), Gangemi, S., et al., Int J Mol Med. 38(4): 1012–1020 (2016).

[9] See Maryland Department of Agriculture, "List of Pesticides Allowed in the Cultivation of Medical Cannabis" as accessed at https://mda.maryland.gov/plants-pests/Pages/pesticide_regulation.aspx (last accessed on March 4, 2020). (copy attached: Appendix B)

[10] See, for example, (copy attached: Appendix C)

[11] See Maryland Medical Cannabis Commission Chart: Flower By Weight January 2020 as accessed at https://mmcc.maryland.gov/Documents/2019%20Retail%20Sales%20Data/01.03.2020.pdf

[12] Sullivan, N., Elzinga, S., and Raber, J. Determination of Pesticide Residues in Cannabis Smoke. J. of Toxicology. 2013: 1-6 (2013).

components found in cannabis smoke,[13] this should not be considered a safe-guard and provides little to none for those smoking medical cannabis with low to no THC. Moreover, there is no scientifically standardized protocol for cannabis pesticide detection at this time.[14] Further, the use of pesticides is not necessary to grow high-quality, affordable medical cannabis.

The United States uses the term 'tolerance' when talking about pesticide levels. How much of that pesticide can the human body handle specific to that pesticide as it interacts with the food product? When it comes to cannabis, the answer is we don't know. There are other times when the answer in cannabis is "we don't know for certain but we know enough to know we're not doing harm." This is not one of those times. We know that pesticides are harmful. We know that even natural or organic pesticides may be harmful in certain amounts or when consumed in particular ways such as combustion. It is believed that there are acceptable levels of pesticides that may be consumed in food products. We know the EPA found that previously acceptable pesticides must be removed due to new scientific data. At best, it is unclear if the application of pesticides to our cannabis can be used with "reasonable certainty of no harm." At best, allowing pesticides into the medical market is high risk. We submit that it is an unnecessary one. These types of pesticides are not necessary to grow the high-quality, affordable medical cannabis that Maryland's qualifying patients need. Safe, natural and organic pesticides exist and produce high-quality, affordable cannabis.

Pesticides, even at EPA acceptable levels, can be harmful to children, the immune-compromised, geriatrics and the chronically ill. The Cannabis Patient Advocacy Association requests either the proposed Maryland Code, Agriculture § 5-105(i) as contained within SB821, be stricken in its entirety or, in the alternative, that it be amended to include the submitted language.

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[13] Taylor, A. & Birkett, J. Pesticides in cannabis: A review of analytical and toxicological considerations. *Drug Test Anal.* 12, 180-190 (2020) (citing Melamede R. Cannabis and tobacco smoke are not equally carcinogenic. *Harm Reduct J.* 2 (21) 1-4 (2005)). (copy attached: Appendix D).

[14] Taylor, A. & Birkett, J. Pesticides in cannabis: A review of analytical and toxicological considerations. *Drug Test Anal.* 12, 180-190 (2020).

Appendix A

Sullivan, N., Elzinga, S., and Raber, J. Determination of Pesticide Residues in Cannabis Smoke. *J. of Toxicology*. 2013: 1-6 (2013).

Research Article

Determination of Pesticide Residues in Cannabis Smoke

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The present study was conducted in order to quantify to what extent cannabis consumers may be exposed to pesticide and other chemical residues through inhaled mainstream cannabis smoke. Three different smoking devices were evaluated in order to provide a generalized data set representative of pesticide exposures possible for medical cannabis users. Three different pesticides, bifenthrin, diazinon, and permethrin, along with the plant growth regulator paclobutrazol, which are readily available to cultivators in commercial products, were investigated in the experiment. Smoke generated from the smoking devices was condensed in tandem chilled gas traps and analyzed with gas chromatography-mass spectrometry (GC-MS). Recoveries of residues were as high as 69.5% depending on the device used and the component investigated, suggesting that the potential of pesticide and chemical residue exposures to cannabis users is substantial and may pose a significant toxicological threat in the absence of adequate regulatory frameworks.

1. Introduction

Cannabis *sativa* L. has been widely utilized by humans for thousands of years for the relief of a wide range of physiological ailments. In the United States, there are currently 18 different states and the District of Columbia that legally allow for the medical use of cannabis, and most recently the states of Colorado and Washington have legalized the use of cannabis by adults for recreational purposes. State lawmakers and regulatory departments are now being tasked to best enact appropriate laws, rules, and regulations on the use of cannabis for both medicinal and recreational purposes. While medicinal use of cannabis in a smoked form may be widely debated as an effective delivery form, rapidity of effect and ease of titration of dose lend it to be extensively used by many patients as their preferred delivery method today. Undoubtedly, recreational use will see considerable consumption via smoking of dried cannabis flowers. In an effort to help aid patients, lawmakers, regulators, and the general public understand the potential harms of contaminated cannabis we sought to determine to what extent pesticide residues may transfer into the mainstream smoke, produced from cannabis, when inhaled through various smoking devices currently being used by medical cannabis patients. Mainstream smoke consists of the smoke inhaled from a smoking device directly while sidestream smoke refers to smoke that otherwise escapes the device and is not directly inhaled.

The ubiquitous use of pesticides in agriculture has earned itself a long history in the United States from the outset of the Insecticide Act passed in 1910 to the now heavily engaged US Environmental Protection Agency (US EPA), Federal Department of Agriculture (FDA), and United States Department of Agriculture (USDA) along with individual state regulators [1]. According to a report issued by the US General Accounting Office (GAO) in 2003, the use of pesticides on tobacco crops was limited to 37 pesticides, which included various organochlorides, organophosphates, and other classes of pesticides. Allowable pesticides and residue levels on food crops are determined by the US EPA, while the testing and monitoring of the presence and levels of residues are conducted by the FDA and USDA. However, since tobacco is not a food crop, the US EPA has not set tolerances on the residue levels on tobacco crops. Consequently, tobacco is only monitored for compliance with US EPA approved pesticides while the residue levels are not federally regulated [2].

To date, there are no approved pesticides or application limits established for use on cannabis crops by the US EPA; therefore, all pesticide use on this crop is currently illegal [3]. The use of pesticides and plant growth regulators in medicinal cannabis cultivation has been found to be quite prevalent by both testing laboratories and authority laboratories alike. Many commercially available pesticide containing products or nutrient systems, some only approved for use on ornamental crops, are widely available from a variety of sources including hardware stores, specialty indoor hydroponic shops, and various, sometimes unscrupulous, online vendors. While 18 states allow cannabis for medicinal use, the majority of the current medical cannabis supply lacks regulations and enforcement related to the quality and safety of the plant material for consumption. Laboratories operating within California have reported that cannabis samples contaminated with residual pesticides are frequently encountered. In 2009 the Los Angeles City Attorney's office covertly acquired and then tested three medical cannabis samples available to patients through dispensaries and found that in two of the samples exceedingly high levels of bifenthrin were found. In one sample, 1600 times the legal digestible amount was measured, and in the other, 85 times the legal limit was measured, although the exact quantities were not stated [4].

Many medical cannabis products are currently cultivated, processed, and prepared by private entities that are not regulated by external agencies. The lack of quality control results in patients potentially being exposed to cannabis contaminated with toxic levels of pesticides. Although not yet directly quantified, additional health complications in patients may become a contingency of pesticide exposure and may also interfere with long-term cannabis use studies. Regardless, pesticide toxicity is well documented [5] and more importantly can pose substantial threats to immuno-compromised patients or patients with other conditions, such as diseases of the liver, that may intensify the toxicological effects of pesticide exposure [6]. Additionally, during heating pyrolysis products from the plant material form a highly complex mixture of products, many of which may interact with the pesticides or pyrolysis products of the pesticides forming more toxic materials, or highly toxic pyrolysis products may form from the pesticide residues alone [7]. As stated in the review by US General Accounting Office (GAO) in 2003, exposure to organophosphate pesticides through inhalation causes the most rapid appearance of toxic symptoms, and the primary cause of death from organophosphate pesticides is respiratory failure [2]. Considering these issues, evaluation of the exposure from contaminated cannabis needs to be urgently addressed so that new regulations can be properly guided.

A previous pesticide study conducted with filtered tobacco cigarettes had positively identified the recovery of pesticides in the mainstream smoke to range from 2 to 16% [8]. Additionally, the distributions of volatilized pesticides and pyrolysis products in tobacco cigarette mainstream smoke and sidestream smoke were found to differ [7]. The mainstream smoke pesticide residues consist primarily of unpyrolyzed pesticides carried over by distillation characteristics related to steam volatility, while in the sidestream smoke, a larger portion of pyrolysis products are found [7]. In the same study, it was determined that about one half of ^{14}C-labeled pesticides were retained in a cotton cigarette filter in a nonselective manner [7]. For the most part, since cigarette filters absorb a significant portion of the volatilized residues and a substantial toxicological threat is already associated with smoking tobacco, little concern for pesticide exposure to tobacco smokers has been considered [2, 7]. Cannabis smoking devices often do not include filtration processes and because of this the potential quantities of pesticide residues that may be consumed increases dramatically when compared with tobacco smoking. In the present study, we chose to evaluate both filtered and nonfiltered smoking devices to better understand this effect with cannabis and commonly employed medical cannabis consumption methods. While it is known that combustion of plant material causes the formation of carcinogens, there has been no direct correlation in the formation of lung cancers to the inhalation of combusted cannabis [8]. The presence of pesticide residues is therefore critical to be monitored, and furthermore, those individuals seeking to use cannabis for medicinal purposes may also be more physiologically susceptible to negative impacts caused by the presence of these residues.

To prevent overtreatment of tobacco with pesticides, certain application limits on crop treatment have been imposed to minimize exposure to tobacco smokers, but these are not fully federally regulated [2, 9, 10]. Industrial and other laboratories have attempted to quantify the levels at which pesticide residues transfer into the smoke stream in order to validate what quantities of pesticides may safely be applied to crops, and these values have been used to help moderate the levels of pesticide exposure of the public [5, 11]. Considering that there currently exists a significant lack of analogous regulations set in place for the medical cannabis supply, it is important that the potential for pesticide exposure is evaluated under conditions commonly employed by the medicinal user. In order to determine the existence of pesticide and chemical residues in the cannabis smoke stream, a number of pesticides and a plant growth regulator which are readily available to cannabis cultivators and have been measured in high frequency in various medical cannabis products (unpublished data, The Werc Shop, Inc., 4) were selected for the study. Three different smoking devices, chosen to provide a broad overview, were used in the study; a small glass pipe, a water pipe, and an identical water pipe outfitted with activated carbon filters and cotton filters.

2. Methods

2.1. Chemicals. Acetonitrile, methanol, and water of analytical grade as well as washing acetone and methanol of laboratory grade were purchased from Sigma Aldrich, St. Louis, MO, USA. Bifenthrin and diazinon were purchased from Chem Service, West Chester, PA, USA. Paclobutrazol and permethrin were purchased from Sigma Aldrich, St. Louis, MO, USA. Virgin coconut carbon and cotton were obtained from Scientific Inhalations, Grass Valley, CA, USA.

2.2. Smoking Devices. The water pipe was manufactured by Scientific Inhalations, Inc. and is named the McFinn Triple Filtered Water Pipe having a vapor flow path consisting of first a 2.5 cm cup for placement of the flower material, followed by a 2.5 cm connector, flowing in to a 10 cm filter, down further into a 15 cm water chamber having a 3.1 cm inner diameter and a water fill line 3.8 cm from the base. The water chamber also has a second 12.5 cm filter chamber connected at a 45° angle through a 5 cm fitting that is located 12.5 cm above the base of the water chamber, and the second arm then further connects to a mouth-piece. A special mouth-piece was custom made by Scientific Inhalations to allow for easy connection to the gas-wash bottle apparatus. The glass pipe was custom made by Scientific Inhalations to be 10.5 cm long with a 3.1 cm chamber diameter and 1.1 cm inner diameter that included a special mouth-piece configuration for easy adaption to the gas-wash bottle apparatus.

2.3. Method for Identification and Quantification of Pesticide Residues by GC-MS. Analysis was conducted with a GCMS-QP2010 PLUS (Shimadzu, Japan) gas chromatograph-mass spectrometer. Separations were performed using a Shimadzu SHRXI-5MS 30 meter, 0.25 mm i.d., and 0.25 um film thickness column. Gas chromatography parameters were as follows: injector temperature 250.0°C, splitless injection mode, column oven temp. 50.0°C held for one minute, followed by an increase to 125°C by 25°C/min, and finally increased to 300°C for 15 minutes by 10°C/min. The column flow was set to 1.69 mL/min 99.999% Helium. MS scan was carried out in selected ion monitoring (SIM) mode with two reference ions for each pesticide to avoid false positives from the complex matrixes. Pesticide calibration curves were prepared in matched matrixes, which were prepared from unspiked plant material using the same smoking procedure used for all the experiments as described in Section 2.6.

2.4. Preparation of Pesticide Spiked Plant Material. Plant material was prepared by first placing approximately 8 grams of homogenized cannabis flower material into a 250 mL round bottom flask and vortexed at 1200 rpm until the small non-leafy material fell to the bottom. This material was then separated and sifted over a rough screen to further remove small non-leafy material. This process was repeated five times until the plant material was sufficiently cleared of fine material that might otherwise incur poor homogeneity of pesticide distribution in the bulk of the material.

To the sifted plant material, a concentrated solution of pesticide mixture in methanol, prepared to contain 0.730 mg/mL bifenthrin, 7.41 mg/mL diazinon, 4.37 mg/mL paclobutrazol, and 6.18 mg/mL permethrin, was then added incrementally to the plant material. These concentrations were selected to allow for full quantification of residues captured in the gas wash bottle solutions. A total of 8.30 mL of the pesticide mixture solution was added to 7.4860 g of the material incrementally. Each increment was carried out by adding 1 mL of the solution drop-wise into a 250 mL round bottom flask containing the plant material that was then vortexed at 1300 rpm over a 2 minute period. After

each mL was added, the flask was then placed on a rotary evaporator and rotated at 50 rpm for 3 minutes while under vacuum. This was repeated until all 8.30 mL were added and then evaporated. The flask was then covered in a dark encasing and stored at −20°C until further used. From the spiked plant material, duplicate samples were prepared and evaluated for homogeneity of the pesticide distribution. The measured values were averaged and this value was used for the recovery calculations in the smoke condensate.

2.5. Apparatus and Method for Condensation and Recovery of Pesticide Residues in Smoke Stream. The smoke stream was collected by being directed through two gas washing bottles which were placed in tandem cold methanol traps both held at −48°C. The gas wash bottles were filled with 100 mL of analytical grade methanol each. The gas wash bottles were then connected with a 6 inch tube in tandem to a vacuum pump intermediated by a gas flow regulator. The end of the system was then fixed to the smoking devices via a frosted glass fitting or direct connection via tygon tubing. A vacuum was applied to the system using a diaphragm vacuum pump (MD 4C, Vacuubrand, Essex, CT, USA) in order to pull smoke from the smoking device and through both of the gas wash bottles.

In order to ensure that the draw rate and vacuum pressure were constant throughout all experiments, a simple device was arranged to monitor the vacuum settings. A long glass column was placed upright in a water vessel filled with a constant volume of water. To the top end of the glass column, a tubing fitting was fixed and vacuum tubing connected. To the tubing, a valve at a constant setting was opened slightly to allow air to enter and prevent the water from being pulled into the vacuum. After having twelve different current medical cannabis patients inhale through the end of a tube attached to the valve while instructed to emulate the draw strength they typically use for these smoking devices, it was determined that the draw rate of an average smoking device user was approximately 1.2 L/min. This draw rate was then used for all of the experiments by ensuring that the vacuum was set to draw at a rate that yielded height in the water column corresponding to 1.2 L/min. This process was performed before, during, and after each experiment to ensure the simulated inhalation flow rate was as consistent as possible.

2.6. Smoking Procedure. The smoking procedure was carried out by passing the flame of a disposable lighter over the plant material for three seconds at 15-second intervals while the vacuum was applied at 1.2 L/min. For each experiment, approximately 0.45 g of spiked cannabis was used. Aliquots from the gas wash bottles were taken after being shaken and agitated to capture any condensate on the walls and stems of the wash bottles and measured with GC-MS. Samples were then stored at −20°C in the absence of light. All glassware, tubing, and smoking devices were then washed thoroughly with methanol and acetone between experiments. In the case of the water pipe, water was used in the water chamber as per manufacturer's specifications, and when applicable,

TABLE 1: Calibration curves and goodness of fit values.

Residue	Range (μg/mL)	Raw plant material matrix	Glass pipe smoke matrix	Water pipe smoke matrix
Diazinon	0.737–36.9	0.9994	0.9994	0.9997
Paclobutrazol	0.437–21.9	0.9994	0.9982	0.9999
Bifenthrin	0.072–3.62	0.9811	0.9998	0.9971
Permethrin	0.607–30.4	0.9915	0.9999	0.9999

TABLE 2: Spiked plant material extractions.

Pesticide	μg/gram plant
Spiked plant material	
Diazinon	6950 ± 5.88
Paclobutrazol	4120 ± 4.46
Bifenthrin	855 ± 3.63
Permethrin	6270 ± 4.69

Data presented as mean μg pesticide/gram plant material ± relative standard deviation. Sample size of 3 for all measurements.

7.5 g of virgin coconut carbon was used in the carbon filter cartridge, while 0.7 g of cotton was used in the cotton filter cartridge. After each experiment using the filtered device, the cotton and carbon were extracted with 15 mL of analytical grade methanol and measured by GC-MS. Experiments were carried out in triplicate for each device.

2.7. Preparation of Calibration Curves. Three sets of calibration curves were prepared, each in different matrixes that consisted of smoked plant material solutions in order to account for possible ion suppression from the matrixes. All matrixes and plant material samples were ensured to be free of the pesticides of interest before use and further analysis. For the preparation of the raw plant material matrix, approximately 4 g of unspiked cannabis plant material from the same source as that which was spiked was extracted with 100 mL of analytical grade methanol and stirred with a stir bar for 20 minutes, followed by filtration through a Buchner funnel. Smoke condensate matrixes from the glass pipe and the water pipe were prepared by running the experiment with each device as described in Section 2.6 and storing the solutions in a dark container at −20°C before analysis. Each of these matrix solutions was then used to dilute the stock solutions of pesticides for generating calibration curves in each matrix.

3. Results

The calibration solutions of chemical residues were prepared in the three separate matrixes and the calibration curves generated are tabulated in Table 1. Table 2 presents the chemical residue content of the spiked plant material. Chemical residues recovered from the smoking devices are tabulated in Table 3, as well as the percent recovery with respect to the spiked plant material. It should be noted that 97% of the recovered residue in the gas wash bottles was found in the

TABLE 3: Recovery of pesticides in smoke condensate.

Sample/residue	μg/gram plant	% Recovery
Water pipe with filters		
Diazinon	589 ± 31.0	0.08
Paclobutrazol	420 ± 32.5	10.2
Bifenthrin	77 ± 34.5	9.00
Permethrin	685 ± 34.9	10.9
Cotton filter		
Diazinon	190 ± 11.0	24.9
Paclobutrazol	109 ± 8.80	30.1
Bifenthrin	20.8 ± 9.16	26.6
Permethrin	134 ± 8.52	25.1
Carbon filter	N/A	N/A
Water pipe w/out filters		
Diazinon	2930 ± 15.1	42.2
Paclobutrazol	2040 ± 11.3	49.5
Bifenthrin	389 ± 10.1	45.4
Permethrin	3760 ± 9.72	59.9
Glass pipe		
Diazinon	4270 ± 12.3	61.5
Paclobutrazol	2789 ± 13.8	67.4
Bifenthrin	516 ± 12.8	60.3
Permethrin	4360 ± 9.70	69.5

Data presented as mean μg pesticide/gram plant material ± relative standard deviation. Sample size of 3 for all measurements.

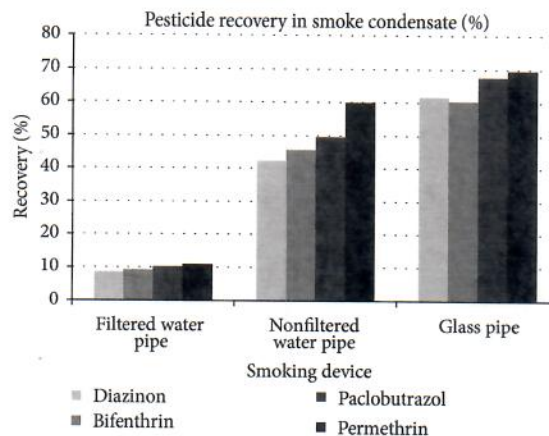FIGURE 1: Percent recovery of pesticides from the smoke stream from each device.

first wash bottle, representing excellent recovery capabilities. In all three experiments, the recovery of chemical residues from the activated charcoal was below the lowest calibration level and is therefore not reported. Figure 1 illustrates the comparative recovery of chemical residues from each of the smoking devices.

4. Discussion

The relative amounts of pesticide residues present in other smoked plant material, most notably tobacco, have been studied to determine the amount present in raw plant material, as well as the levels of transfer into the smoke stream. These results have been used to help guide regulations on pesticide application on tobacco crops and reduce the potentials of pesticide toxicity in consumers [9, 12, 13]. As medical cannabis patients already possess negative health complications, exposure to pesticides may create additional health complications and interfere with other health care approaches. In addition, the awareness of proper and safe pesticide use and application is very important to any crop that will be consumed, especially one that will be inhaled. Understanding to what extent chemical residues may be consumed by the user of the final product is important, but also improper applications of pesticides on cannabis crops may lead to other contingencies such as applicator exposure and environmental contamination. To bring attention to the importance of pesticide awareness and to further the regulatory efforts for both the medical cannabis and impending recreational cannabis supplies, the present study demonstrates quantitatively the potential for pesticides to be transferred into the smoke stream under the conditions often encountered by cannabis users. While the variance between triplicate samples was notable, when considering the vast number of variables including heating conditions, and other inherent variations, the overall variation was fairly minimal.

From the data presented here, the recoveries of pesticide residues in the smoke stream are very significant in relation to the potential of exposure by the end consumer. A previous study with filtered tobacco cigarettes published by Cai et al. [9] noted that the range of pesticide recovery from the smoke stream was 2 to 16%. The range of pesticide residue recovery in that study was comparable to the water pipe with filters (0.08–10.9%) used in the present study, but without filters the recovery from the present study was much higher as evident in Table 3 and Figure 1. This suggests that the cotton filters in a cigarette or water pipe are critical in capturing and reducing pesticide residues in the mainstream smoke. Also, extractions of the cotton filters (Table 3) contained a significant portion of the pesticides passed through the device. The carbon filter retained an insignificant amount of pesticides, but this may have been due to heating and desorption of retained compounds during each use as this portion is closest to the plant material combustion point. Between the glass pipe and the water pipe with no filters, the relative pesticide recovery was greater when the glass pipe was used. This difference may be attributed to the comparable levels of surface area for the residues to accumulate inside the device by condensation, as well as factors such as total path length, smoke stream total flow rate velocity, and the absolute temperatures achieved in situ. Additionally, the water pipe contained room temperature water that aids in cooling the smoke stream before exiting the device. Comparative recoveries between individual pesticides (Figure 1) show significant differences in the recovery of each pesticide. These differences may be attributed to the variations in stability of each compound,

volatilization characteristics, and to what extent degradation occurs during heating and combustion of the plant material surface.

It should be noted that different levels of pesticides present on different varietals of cannabis flowers present different matrixes that may impact the amount of pesticides potentially being inhaled. Different user behaviors including depth of breath, length of inhalation hold time, and choice of heating method may also impact overall individual exposure amounts. In our lab we use validated methods to detect pesticides above EPA-based acceptable daily intake levels for a 40 Kg individual consuming 10 g of flower material per day. While these limits represent residues on plant material at levels lower than the levels utilized in this study, a number of samples seen have failed considerably further supporting previous findings by local authorities [4]. Additional efforts are ongoing to quantify the amount of pesticides being detected in contaminated medical cannabis products.

5. Conclusion

The present study clearly demonstrates that chemical residues present on cannabis will directly transfer into the mainstream smoke and ultimately the end user. Recoveries occurred in the highest quantity with the hand-held glass pipe, ranging between 60.3% and 69.5%. Recovery from the unfiltered water pipe ranged between 42.2% and 59.9%, and recovery from the filtered water pipe ranged between 0.08% and 10.9%. As mentioned previously, the effects of filtration have a significant impact on the total residues consumed. While there are differences between the devices, in general the portion of pesticide recovery is alarmingly high and is a serious concern. Although pesticides are designed to degrade fairly quickly in the environment [14], it is evident from this study that some are highly resistant to pyrolysis and volatilize easily into the smoke stream in agreement with previous studies noting the distillation behavior of pesticides in mainstream smoke [7]. Considering these results, high pesticide exposure through cannabis smoking is a significant possibility, which may lead to further health complications in cannabis consumers. This revelation certainly confounds previous metastudies seeking to determine the possible negative consequences associated with long-term cannabis use, as our experience with a breadth of samples indicates a significant possibility that the negative consequences reported in these studies could have been the result from various chemical residue exposures resulting from the use of unregulated product supply chains. As more states legislate and regulate cannabis products, a strong regulatory approach will help to reduce the potential public health and safety consequences from pesticide exposure. While it is fortunate that chemical residue recovery may be minimized with smoke filtering, this only serves to improve consumer safety today with no adequate regulations, as there is no better way to avoid pesticide and other chemical residue consumption than to assure it is not present on the product in the first place. Active sampling and analytical monitoring of the cannabis supply, along with collaborative efforts between current patients and state regulatory authorities, are needed

to help further guide the development and implementation of proper application methods and testing standards that will avoid environmental contamination and consumer threats to public health and safety.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

References

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<u>Appendix B</u>

Maryland Department of Agriculture, "List of Pesticides Allowed in the Cultivation of Medical Cannabis" as accessed at <u>https://mda.maryland.gov/plants-pests/Pages/</u> <u>pesticide_regulation.aspx</u>

Maryland Product Name	EPA Number	Pesticide Type
70% Neem Oil (Monterey)	70051-2-54705	Fungicide, Insecticide
Actino-Iron Biological Fungicide	73314-2	Fungicide
Actinovate AG	73314-1	Fungicide
Actinovate SP	73314-1	Fungicide
Agree WG	70051-47	Insecticide
Agri-Fos Systemic Fungicide	71962-1	Fungicide
Agri-Fos Systemic Fungicide	71962-1-54705	Fungicide
Alude Fugicide	55146-83	Fungicide
Alude Systemic Fungicide	71962-1-1001	Fungicide
Axiom	71771-3-89112	PGR
Aza-Direct Biological Insecticide	71908-1-10163	Insecticide
AzaGuard	70299-17	Insecticide
AzaSol	81899-4-74578	Insecticide
Azatin O Biological Insecticide	70051-9-59807	IGR
Biobit HP Biological Insecticide Wettable Powder	73049-54	Insecticide
BioSafe Disease Control (Concentrate)	70299-16	Fungicide
BioSafe Disease Control RTU	70299-9	Fungicide
BioSafe Insect Control	70299-17	Insecticide
Bio-Tam 2.0	80289-9	Fungicide
Bonide Insecticidal Soap Multipurpose Insect Control Concentrate	67702-11-4	Insecticide
Bonide Insecticidal Soap Multi-Purpose Insect Control Ready To Use	67702-13-4	Insecticide
Bonide Mite X Ready to Use	25(b)	Miticide
Bonide Slug Magic	67702-1-4	Molluscicide
Botanical Concentrated Bacteriostat & Fungistat	25(b)	Hard surface disinfectant
BotaniGard ES	82074-1	Insecticide, Miticide
BotaniGard 22WP	82074-2	Insecticide
Camelot O	67702-2-67690	Fungicide
Captiva	10163-326	Insect Repellent
Captiva Prime	10163-336	Insecticide
Cease	264-1155-68539	Fungicide
Companion Liquid Biological Fungicide	71065-3	Fungicide
Corry's Slug & Snail Killer	67702-33-8119	Molluscicide
Cueva Fungicide Concentrate	67702-2-70051	Fungicide
Debug Turbo	70310-5	Fungicide, Insecticide, Nematicide
Des-X Insecticidal Soap Concentrate	67702-22-70051	Insecticide
Dipel DF Biological Insecticide Dry Flowable	73049-39	Insecticide
DiTera DF Biological Nematicide	73049-67	Nematicide
Double Nickel LC	70051-107	Fungicide
DoubleNickel55	70051-108	Fungicide
Drexel Phiticide	19713-625	Fungicide
Earth-tone Insecticidal Soap	67702-21-83598	Insecticide
Eco-1 Garden Spray Concentrate	25(b)	Miticide, Insecticide
Ecozin Plus 1.2% ME	5481-559	Insecticide
Eliminator Snail & Slug Killer	67702-32-59144	Molluscicide
Fungi-Phite	73771-5	Fungicide
Garden Safe Brand Neem Oil Extract Concentrate	70051-2-39609	Fungicide, Insecticide, Miticide

General Hydroponics Defguard Biofungicide/Bactericide	91865-3	Fungicide
General Hydroponics Exile Insecticide/Fungicide/Miticide	91865-2	Fungicide, Insecticide, Miticide
General Hydroponics Prevasyn Insect Repellent/Insecticide	91865-1	Insect Repellent, Insecticide
GibGro 4LS	55146-62	PGR
Grandevo CG	84059-27	Insecticide
Grandevo PTO	84059-17-87865	Insecticide
Grandevo WDG	84059-27	Insecticide
Javelin WG Biological Insecticide	70051-66	Insecticide
Milstop Broad Spectrum Foliar Fungicide	70870-1-68539	Fungicide
Molt-X	68539-11	Insecticide
Monterey Complete Disease Control Brand	70051-107-54705	Fungicide
Monterey Complete Disease Control Brand RTU	70051-114-54705	Fungicide
Monterey Garden Phos	83416-1-54705	Fungicide
M-Pede Insecticide Miticide Fungicide	10163-324	Fungicide, Insecticide
Mycostop WP	64137-5	Fungicide
Mycotrol ESO	82074-1	Insecticide
Mycotrol WPO	82074-2	Insecticide
Natural Guard Brand by Ferti-lome Insecticidal Soap Concentrate	67702-22-7401	Insecticide
Natural Guard Brand by Ferti-lome Neem	70051-2-7401	Insecticide, Miticide
Natural Guard Brand Neem	70051-2-7401	Insecticide
Neemix 4.5 Insect Growth Regulator	70051-9	Nematicide
NimBioSys Neem Oil (Ag Use)	84181-2	Insecticide
Optify/Stretch	33270-40	PGR
Organic JMS Stylet-Oil	65561-1	Fungicide, Miticide, Virucide, Insecticide
Organocide 3-in1 Graden Spray	25(b)	Insecticie, Fungicide, Miticide
Organocide Plant Doctor	71962-1-70179	Fungicide
Ornazin 3% EC Botanical Insecticide	5481-476-67690	Insecticide
OxiDate 2.0	70299-12	Fungicide
OxiPhos	70299-22	Bactericide/Fungicide
Perpose Plus	86729-1	Algaecide, Fungicide
Phostrol Agricultural Fungicide	55146-83	Fungicide
Preferal	70051-19-67690	Insecticide
PreFense Biofungicide	64137-5-68539	Fungicide
Prescription Treatment brand Ultra-Pure Oil	69526-5-499	Fungicide, Insecticide, Miticide
Pro-Mix Biofungicide + Mycorrhizae	74267-4	Fungicide
Pro-Mix BRK Biofungicide + Mycorrhizae	74267-4	Fungicide
Pro-Mix BRK20 Biofungicide + Mycorrhizae	74267-4	Fungicide
Pro-Mix BX Biofungicide + Mycorrhizae	74267-4	Fungicide
Pro-Mix HP Biofungicide + Mycorrhizae	74267-4	Fungicide
Pro-Mix HPCC Biofungicide + Mycorrhizae	74267-4	Fungicide
Rampart Fungicide	34704-924	Fungicide
Regalia CG	84059-3	Fungicide
Regalia PTO Biofungicide	84059-3-87865	Fungicide
Reliant Systemic Fungicide	83416-1	Fungicide
Rootshield Plus Granules	68539-10	Fungicide
Rootshield Plus WP	68539-9	Fungicide
Safer Brand 3-in-1 Concentrate II	59913-13	Fungicide, Insecticide, Miticide

Safer Brand Insect Killing Soap ConcentrateII	42697-60	Insecticide
Sanidate 5.0	70299-19	Hard surface disinfectant
Serenade Garden Disease Control Concentrate	264-1152	Fungicide
Serenade Garden Disease Control Ready to Spray	264-1152	Fungicide
Serenade Garden Disease Control Ready to Use	264-1154	Fungicide
Suffoil-X	48813-1-68539	Insecticide, Miticide
Suppress Herbicide EC	51517-9	Herbicide
Sysstem-K Blue Agricultural Fungicide	48222-10	Fungicide
Tenet WP	80289-9	Fungicide
TerraClean 5.0	70299-13	Antimicrobial, Fungicide
TerraStart	70299-18	Antimicrobial, Fungicide
Triact 70	70051-2-59807	Fungicide, Insecticide, Miticide
Triathlon BA	70051-107-59807	Fungicide
Trilogy	70051-2	Fungicide, Insecticide
Triple Action Neem Oil	70051-2-829	Fungicide, Insecticide, Miticide
Valent Professional Products DiPel Pro DF Biological Insecticide Dry Flowable	73049-39	Insecticide
Venerate XC	84059-14	Insecticide
XenTari Biological Insecticide Dry Flowable	73049-40	Insecticide
ZeroTol 2.0	70299-12	Antimicrobial, Fungicide
ZeroTol HC	70299-16	Fungicide, Bacteriocide, Algacide
Zonix Biofungicide	72431-1	Fungicide

Safety Data Sheet for Debug Turbo

EPA Number 70310-5

Pesticide Type: Fungicide, Insecticide, Nematicide

SAFETY DATA SHEET FOR DEBUG TURBO

1.IDENTIFICATION

PRODUCT IDENTIFIER:	**DEBUG TURBO**
NAME & ADDRESS OF MANUFACTURER:	**AGRO LOGISTIC SYSTEMS INC.**
	555 WEST LAMBERT ROAD, UNIT-N
	BREA, CA 92821
EMERGENCY PHONE NUMBER:	**714-990-9220**
RECOMMENDED USE:	**COLD PRESSED NEEM OIL AND AZADIRACHTIN BASED AGRICULTURAL SPRAY BOTANICAL INSECTICIDE, MITICIDE, NEMATICIDE, FUNGICIDE, INSECT REPELLANT, AND ANTIFEEDANT. APPROVED FOR USE IN ORGANIC FARMING.**

2. HAZARDS IDENTIFICATION

NONE AS PER 29 CFR PART 1910.1200 or SARA 313
THIS PRODUCT IS INTENDED FOR USE AS AN ANTIFEEDANT, INSECT REPELLENT, GROWTH REGULATOR AND AS A PESTICIDE TO CONTROL INSECTS ON AGRICULTURAL CROPS. APPROVED FOR USE IN ORGANIC FARMING. THIS PRODUCT SHOULD NOT POSE ANY HEALTH CONCERNS IF USED IN ACCORDANCE WITH THE LABEL DIRECTIONS.
SIGNAL WORD-CAUTION
HAZARD STATEMENTS:

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS
Harmful if absorbed through skin or if inhaled. Causes moderate eye irritation. Avoid breathing spray. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.

Personal Protective Equipment (PPE)
Applicators, Mixers and other handlers must wear
-Coveralls
- Socks, shoes, and
-Chemical resistant gloves.
Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables use detergent and hot water. Keep and wash PPE separately from other laundry

USER SAFETY RECOMMENDATIONS
Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

ENVIRONMENTAL HAZARDS
For terrestrial uses: Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwater or rinsate.
This product is toxic to fish and aquatic invertebrates. Drift or runoff may be hazardous to aquatic organisms in water adjacent to treated areas.

3.COMPOSITION / INFORMATION ON INGREDIENTS

CHEMICAL NAME: AZADIRACHTIN AND NEEM OIL
COMMON NAME AND SYNONYMS: COLD PRESSED NEEM OIL AND AZADIRACHTIN

Component	CAS#	WT.%	OSHA PEL	TWA	TLV'S STEL
FATS AND GLYCERIDIC OILS, MARGOSA	8002-65-1	65.80	N/A	N/A	N/A
AZADIRACHTIN	11141-17-6	0.70	N/A	N/A	N/A
OTHER INGREDIENTS		33.50	N/A	N/A	N/A

4.FIRST AID MEASURES

	FIRST AID
If on skin or clothing	Take off contaminated clothing. - Rinse skin immediately with plenty of water for 15-20 minutes - Call a poison control center or doctor for treatment advice.
If inhaled	-- Move person to fresh air. - If person is not breathing call 911 or an ambulance, then give artificial respiration, preferably mouth to mouth if possible. - Call a poison control center or doctor for further treatment advice

HOT LINE NUMBER
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For emergency information concerning this product, call the National Pesticides Information Center (NPIC) at 1-800-858-7378 seven days a week, 6:30AM to 4:30PM Pacific Time (NPIC Web Site: www.npic.orst.edu).

5.FIRE FIGHTING MEASURES

FLASH POINT:	NA
FLAMMABLE LIMITS:	NA
EXTINGUSHING MEDIA:	WATER, CO_2, POLYMER FOAM
SPECIAL PROCEDURES FOR FIRE FIGHTING:	FIRE FIGHTERS SHOULD BE EQUIPPED WITH SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING.
UNUSUAL HAZARDS:	FLAMMABLE LIQUID. KEEP AWAY FROM OPEN FLAME, HEAT OR SPARKS.
NFPA HAZARD CLASSIFICATION:	HEALTH HAZARD 1 FIRE HAZARD 3
	REACTIVITY 0

6,ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN THE EVENT OF A SPILL OR DISCHARGE:

TAKE UP WITH SAND OR OTHER ABSORBANT MATERIAL AND PLACE IN CONTAINER FOR LATER DISPOSAL. WASH DOWN THE AREA WITH WATER

DISPOSAL PROCEDURE:

BURY OR INCINERATE IN ACCORDANCE WITH ALL APPLICABLE FEDERAL, STATE, AND LOCAL ENVIRONMENTAL REGULATIONS.

VENTILATION:	USE ADEQUATE GENERAL LOCAL EXHAUST VENTILATION TO KEEP VAPOR OR MIST LEVELS AS LOW AS POSSIBLE.
RESPIRATORY PROTECTION:	NONE REQUIRED WHERE ADEQUATE VENTILATION CONDITIONS EXIST. IF AIRBORNE CONCENTRATION IS HIGH, USE AN APPROPRIATE RESPIRATOR OR DUST MASK.
EYE/ SKIN PROTECTION:	SAFETY GOGGLES, CHEMICAL RESISTANT GLOVES, COVERALLS, SHOES AND SOCKS.

7.HANDLING AND STORAGE

SPECIAL PRECAUTIONS:	KEEP CONTAINER TIGHTLY CLOSED. STORE IN A COOL AND DRY PLACE. SUITABLE FOR ANY GENERAL CHEMICAL STORAGE AREA. AVOID PERSONAL CONTACT AND HANDLE WITH CARE IN ACCORDANCE WITH GOOD INDUSTRIAL PRACTICES.

8.EXPOSURE CONTROLS/PERSONAL PROTECTION

CARCINOGENICITY:	NTP: NO IARC: NO Z LIST: NO OSHA REG: NO
EFFECTS OF OVEREXPOSURE:	NOT KNOWN
TARGET ORGANS:	NONE IDENTIFIED
ROUTES OF ENTRY:	INHALATION, INGESTION, SKIN CONTACT, EYE CONTACT, ABSORPTION.

TOXICOLOGICAL INFORMATION:

ORAL LD_{50} = >5000 mg/kg; DERMAL LD_{50} = >2000 mg/kg; INHALATION LC_{50}= >1.34 mg/liter
DERMAL IRRITATION= Non Irritant; ACUTE EYE IRRITATION= Non Irritant; SKIN SENSITIZATION: Non sensitizer

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

Harmful if absorbed through skin or if inhaled. Causes moderate eye irritation. Avoid breathing spray. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.

Personal Protective Equipment (PPE)
Applicators, Mixers and other handlers must wear
-Coveralls
- Socks, shoes, and
-Chemical resistant gloves.
Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables use detergent and hot water. Keep and wash PPE separately from other laundry

USER SAFETY RECOMMENDATIONS
Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

9.PHYSICAL CHEMICAL PROPERTIES

APPEARANCE:	DARK BROWN LIQUID
UPPER/LOWER FLAMMABILITY	209 DEGREES F
ODOR:	CHARACTERISTIC NUTTY ODOR
VAPOR PRESSURE:	N/A
pH:	6.6 TO 7.0
RELATIVE DENSITY:	0.893
MELTING/FREEZING POINT:	LIQUID/ 60 DEGREES F
SOLUBILITY IN WATER:	DISPERSIBLE
BOILING POINT:	>300°F
FLASH POINT:	209 DEGREES F
EVAPORATION RATE:	N/A
PARTITION COEFFICIENT:	N/A
AUTO-IGNITION TEMPERATURE:	N/A
DECOMPOSITION TEMPERATURE:	N/A
VISCOSITY:	0.048 KGS/MS
STORAGE STABILITY:	STABLE AT ROOM TEMPERATURE FOR 24 MONTHS.
STABILITY:	STABLE
CONDITIONS TO AVOID:	NONE DOCUMENTED
INCOMPATIBLES:	NONE
POLYMERIZATION:	WILL NOT OCCUR
DECOMPOSITION PRODUCTS:	CARBON MONOXIDE

10.STABILITY AND REACTIVITY

REACTIVITY DATA:

STABILITY:	STABLE
CONDITIONS TO AVOID:	NONE DOCUMENTED
INCOMPATIBLES:	NONE
POLYMERIZATION:	WILL NOT OCCUR
DECOMPOSITION PRODUCTS:	CARBON MONOXIDE
CHEMICAL STABILITY:	STABLE UNDER AMBIENT TEMPERATURE
STABILIZER:	NONE REQUIRED
PHYSICAL APPEARANCE:	UNCHANGED UNDER AMBIENT TEMPERATURE

OTHER:

POLYMERIZATION:	WILL NOT OCCUR
CONDITIONS TO AVOID:	EXTREME COLD AS PRODUCT WILL SOLIDIFY
INCOMPATIBLE MATERIALS:	COPPER PRODUCTS, ALKALINE PRODUCTS
HAZARDOUS DECOMPOSITIONS PRODUCTS	NONE

11.TOXICOLOGICAL INFORMATION

ROUTES OF EXPOSURE:	INHALATION, INGESTION, SKIN CONTACT, EYE CONTACT, ABSORPTION
EFFECTS OF OVEREXPOSURE:	NOT KNOWN
TARGET ORGANS:	NONE IDENTIFIED

CARCINOGENICITY:

NTP:	NO
IARC:	NO
Z LIST:	NO
OSHA REG:	NO
ORAL LD$_{50}$	=>5000MG/KG
DERMAL LD$_{50}$	=> 2000 MG/KG
INHALATION LC$_{50}$:	=>1.34 MG/LITER
DERMAL IRRITATION:	NON IRRITANT
ACUTE EYE IRRITATION:	NON IRRITANT
SKIN SENSITIZATION:	NON SENSITIZER

Harmful if absorbed through skin or if inhaled. Causes moderate eye irritation. Avoid breathing spray. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.

12.ECOLOGICAL INFORMATION

ENVIRONMENTAL HAZARDS
For terrestrial uses: Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwater or rinsate.

This product is toxic to fish and aquatic invertebrates. Drift or runoff may be hazardous to aquatic organisms in water adjacent to treated areas.

PARTITION COEFFCIENT:	LOW KOW (OCTANOL/WATER)
OZONE LAYER DEPLETION POTENTIAL:	NONE
GLOBAL WARMING POTENTIAL:	NONE
BIODEGRADATION:	2 YEARS SHELF STORAGE LIFE AT AMBIENT TEMPERATURE.

13.DISPOSAL CONSIDERATIONS

DO NOT CONTAMINATE WATER, FOOD, OR FEED BY STORAGE AND DISPOSAL.
PESTICIDE STORAGE: KEEP IN ORIGINAL PACKAGING IN COOL AND DRY PLACE AWAY FROM SUNLIGHT AND FOODSTUFFS.
DO NOT REFRIGERATE.
FOR COMMERCIAL AGRICULTURAL USE:
PESTICIDE DISPOSAL: WASTES RESULTING FROM THE USE OF THIS PRODUCT MAY BE DISPOSED OF ON-SITE OR AT AN APPROVED WASTE DISPOSAL FACILITY.
CONTAINER DISPOSAL: Nonrefillable Container. Do not reuse or refill this container. Triple rinse (or equivalent) promptly after emptying. Triple rinse as follows: Empty the remaining contents into the application equipment or a mix tank and drain for 10 seconds after the flow begins to drip. Fill the container full with water and recap. Shake for 10 seconds. Pour rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. Then offer for recycling, if available, or puncture or dispose of in a sanitary landfill, or by incineration. Do not burn unless allowed by state and local ordinances.

14.TRANSPORT INFORMATION

UN NUMBER:	NONE
UN PROPER SHIPPING NAME:	NONE
TRANSPORT HAZARD CLASS:	N/A
PACKAGING GROUP NUMBER:	NONE
ENVIRONMENTAL HAZARDS:	For terrestrial uses: Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwater or rinsate. This product is toxic to fish and aquatic invertebrates. Drift or runoff may be hazardous to aquatic organisms in water adjacent to treated areas.
GUIDANCE FOR TRANSPORT IN BULK:	DO NOT TRANSPORT IN BULK
TECHNICAL SHIPPING NAME:	NEEM OIL
DOT LABEL:	NONE
DOT PLACARD:	NONE

IATA : Non Regulated

15.REGULATORY INFORMATION

EPA- PRECAUTIONARY LABELLING

SIGNAL WORD- CAUTION

HARMFUL IF ABSORBED THROUGH SKIN OR IF INHALED. CAUSES MODERATE EYE IRRITATION. AVOID CONTACT WITH SKIN, EYES OR CLOTHING. AVOID BREATHING SPRAY. REMOVE CONTAMINATED CLOTHING AND WASH CLOTHING BEFORE REUSE. WASH THOROUGHLY WITH SOAP AND WATER AFTER HANDLING.

DO NOT APPLY DIRECTLY TO WATER, OR TO AREAS WHERE SURFACE WATER IS PRESENT OR TO INTERTIDAL AREAS BELOW THE MEAN HIGH WATER MARK. DO NOT CONTAMINATE WATER WHEN CLEANING EQUIPMENT OR DISPOSING OF EQUIPMENT WASH WATERS OR RINSATE. THIS PRODUCT IS TOXIC TO FISH AND AQUATIC INVERTIBRATES

16.OTHER INFORMATION_

LABEL NAME:	DEBUG TURBO
LABEL ADDRESS:	AGRO LOGISTIC SYSTEMS, INC.
	555 W. LAMBERT ROAD, UNIT-N
	BREA, CA 92821
	USA
LABEL TELEPHONE:	714-990-9220
LABEL FAX:	714-990-9222
LABEL e-mail:	info@agrologistic.com

THE INFORMATION AND RECOMMENDATIONS CONTAINED HEREIN ARE BASED UPON DATA BELIEVED TO BE CORRECT. HOWEVER, NO GUARANTEE OR WARRANTY OF ANY KIND EXPRESSED OR IMPLIED, IS MADE WITH RESPECT TO THE INFORMATION CONTAINED HEREIN. THIS SAFETY DATA SHEET WAS PREPARED TO COMPLY WITH THE OSHA HAZARD COMMUNICATION STANDARD (29 CFR 1910.1200 [g]), REVISED IN 2012. THIS SUPERCEDES ANY PREVIOUS INFORMATION.

DATE: MARCH 16.2016

Appendix D

Taylor, A. & Birkett, J. Pesticides in cannabis: A review of analytical and toxicological considerations. *Drug Test Anal.* 12, 180-190 (2020).

WILEY

Pesticides in cannabis: A review of analytical and toxicological considerations

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Abstract

A review of the literature surrounding the use, analysis, and detection of pesticide material for cannabis cultivation is presented. The use of pesticides in crop cultivation is not new, and cannabis crops are no exception. Studies have found that the use of these are common and that high levels of the pesticides are transferred into the cannabis smoke. The most common pesticide classes associated with cannabis are insecticides, acaricides, and fungicides. Over 350 different pesticide products may be used on cannabis materials and of these, 16 pesticides and three plant growth regulators (PGR) are considered to be the main candidates. Many of the pesticides found in cannabis samples destined for consumption are classed as moderately hazardous by the World Health Organization. Analytical methods for pesticide detection on cannabis are being developed with a view to implementing quality control of cannabis, where it is legal, before being sold. However, no standardized protocol exists. The pesticide levels found in the cannabis samples tested were generally low (less than μg/g), these results do not, however, provide information on chronic low-dose adverse effects of pesticides in relation to cannabis consumption. Currently no research exists on the toxicity of pyrolyzed pesticides in humans from smoking cannabis. More studies are needed to further understand this potentially harmful health threat.

KEYWORDS
cannabis, GC–MS, LC–MS/MS, pesticides, toxicity

1 | INTRODUCTION

Cannabis is the most widely used drug globally. Between 2010 and 2016, 145 countries reported growing cannabis on a regular basis. Smoking herbal cannabis is the most common method of administering this drug. Cannabis is currently a class B controlled substance in the UK.[1] The UK government was reluctant to legalize this drug for medical use until recently. Expert doctors have been given permission to issue prescriptions for cannabis-based medicines since 1 November 2018.[2] Ironically, the UK produced 45% of the total legal cannabis destined for medical use in 2016.[3] In the USA, cannabis is federally prohibited for any use under the Controlled Substances Act (CSA) 1970. However, it is legal for medicinal and/or recreational purposes in 50% of the states. This causes much confusion among patients and

healthcare providers.[4] This plant has acquired substantial attention in recent years as an increasing number of countries are legalizing the drug for medicinal as well as recreational use.[5]

Cannabis, similarly to other plants, is prone to diseases, pests, fungi, and bacterial infections. Due to its increasing popularity, especially in countries and states where it is now legal for both medicinal and recreational purposes, growers are more inclined to use plant growth stimulators and pesticides to increase and accelerate the yield.[6] This issue has been widely overlooked since cannabis is still illegal in most parts of the world. There is both a lack of monitoring for the use of pesticides on legal cannabis plantations as well as a lack of knowledge on how pesticides that have undergone pyrolysis in cannabis affect the smoker. Few studies bridge this gap between the detected residue levels and internal doses of pesticides resulting from

the usage of cannabis products.[7] There are currently no accredited or verified methods to test cannabis for pesticides and very little data are published on this topic.[8]

This review aims to assess current data with respect to pesticides used on cannabis materials. Analytical procedures that can detect these chemicals within a cannabis sample are documented and evaluated. Finally, the toxicological implications of smoking pesticide-laced cannabis are discussed.

2 | PESTICIDES

Pesticides are classed into seven major groups: insecticides, herbicides, fungicides, rodenticides, acaricides, molluscicides, and nematocides. This classification is based on the field of use, however, they can also be classified by chemical class. There are organophosphorus compounds (OP), carbamates, chlorinated hydrocarbons, pyrethroids, and heterocyclic compounds. Figure 1 shows examples of the variable structures of the selected pesticides based on their classification.

Most of these can be used on a variety of different targets. Commercial formulations may even mix compounds from these different classes into one product.[9] Numerous pesticides are notorious for their negative health impact on humans and the environment, resulting in their restricted use or a total ban. The acute toxic effects of pesticides following a high dose oral exposure are well documented. Although pesticides may not pose an immediate threat to consumers in small quantities, chronic low-dose adverse effects could be substantial, yet knowledge on this subject is limited.[10] Since cannabis is mainly smoked, the guidelines and reported toxic levels of pesticides risk being inexact, as these levels are associated with agricultural products that are destined to be orally ingested.[11] It has been reported by the Cannabis Safety Institute "that pesticide residue on retail cannabis products is often found at levels exceeding the allowable levels on any agricultural product".[12] Moreover, it is reported that the metabolites of many pesticides are more toxic than their parent compounds.[9] A study by Dryburgh et al. highlighted that pesticide metabolites will more than likely be present when cannabis is smoked.[13] Most pesticides target the central nervous system and thus could affect more than just the intended pest posing a health threat to humans and other animals.[14] Pesticides may present a danger to users with epilepsy and other neurological conditions by binding to certain receptors in the brain. This could pose a significant threat to medicinal cannabis users who already have negative health complications.[15]

2.1 | Pesticides associated with cannabis

The most common pests associated with indoor cannabis flowers and leaves are aphids, spider mites, and thrips.[16] Fungal diseases are also problematic in greenhouses and when using indoor lighting systems. Consequently, the most common pesticides associated with cannabis are insecticides, acaricides, and fungicides.[17] Cannabis is an illegal drug in most countries, therefore there are no guidelines for pesticide use on cannabis cultivation. In the countries where it is legal, whether that be for medicinal or recreational use, the originality of the situation means that no guidelines currently exist.[18] Moreover, many legislations do not prioritize this issue in the routine analysis of cannabis samples. A study found that 44% of 1722 growers in Australia, Denmark, and the UK admit to using chemical fertilizers, supplements, or insecticides.[19] This is a large number, taking into account that some growers may not have taken part in the survey due to the fear of being discovered. A recent study examining legalized cannabis products in Washington State found that 84.6% of the samples contained significant quantities of pesticide residues, although no concentrations were mentioned.[20] Medical cannabis products tested in California had pesticides in 49.3% of the samples.[21] In the USA, it is illegal to use a pesticide on a crop that it is not specifically designed for.[22] The Environmental Protection Agency (EPA) claims: "We have yet to receive any applications for pesticide use on marijuana and therefore, have not evaluated the safety of any pesticide on marijuana".[23] Furthermore, setting tolerance limits is complex and time-consuming. In the absence of federal regulations, states have individually formulated guidelines.[24]

The Washington State Department of Agriculture (WSDA) has recently released a list of 271 pesticide products approved for use on cannabis.[17] The state of Colorado has compiled a list of 357 pesticide products, many of which contain the same active ingredients, that are legal to use on cannabis plantations.[24] Historically, some of these pesticides have been approved for use on landscape plants, not plants destined for consumption.[25]

It is believed that indoor plants are at a higher risk of pesticide contamination as opposed to plants grown outdoors.[26] Most cannabis
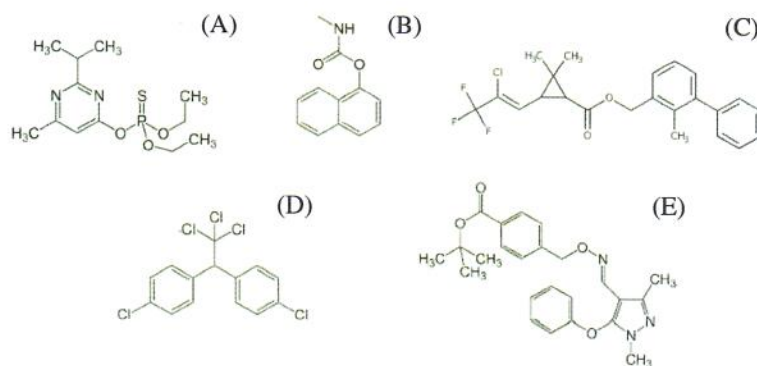

FIGURE 1 Pesticides from different chemical classes, showing pesticide variability. (A) Diazinon (OP); (B) Carbaryl (carbamate); (C) Bifenthrin (pyrethroid); (D) DDT (chlorinated hydrocarbon/organochlorine); (E) Fenpyroximate (heterocyclic compound)

TABLE 1 Pesticides detected in herbal cannabis samples in various countries

Reference	Country	Pesticide	Level detected	WHO oral toxicity in rats[11]
28	Luxembourg	Bifenthrin (insecticide)	60 mg/kg	LD_{50} 50–300 mg/kg, moderately hazardous
		DMST (tolylfluanid metabolite, fungicide)	53 mg/kg	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
		Hexythiazox (acaricide)	0.46 mg/kg	LD_{50} 2000–5000 mg/kg, unlikely to present acute hazard
		Imidacloprid (insecticide)	80 mg/kg	LD_{50} 300–2000 mg/kg, moderately hazardous
		Propamocarb (fungicide)	9.8 mg/kg	LD_{50} 2000–5000 mg/kg, unlikely to present acute hazard
		Propiconazole (fungicide)	No levels given, below the reporting limit	LD_{50} 1520 mg/kg, moderately hazardous
		Tebuconazole (fungicide)	800 mg/kg	LD_{50} 300–2000 mg/kg, moderately hazardous, possible carcinogen
12	Oregon (USA)	Azadirachtin (insecticide)	7.2–36 mg/kg	LD_{50} > 5000 mg/kg[iii]
		Bifenthrin (insecticide)	4.9–5.6 mg/kg	LD_{50} 50–300 mg/kg, moderately hazardous
		Dichlorvos (insecticide)	8 mg/kg	LD_{50} 56 mg/kg, highly hazardous
		Imidacloprid (insecticide)	15.3–64 mg/kg	LD_{50} 300–2000 mg/kg, moderately hazardous
		Myclobutanil (fungicide)	8 mg/kg	LD_{50} 1600 mg/kg, moderately hazardous
6	Washington (USA)	Boscalid (fungicide)	0.15–81.79 mg/kg	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
		Dinotefuran (insecticide)	1.20–13.44 mg/kg	LD_{50} 2000 mg/kg[i]
		Diuron (herbicide)	0.06 mg/kg	LD_{50} 3400 mg/kg, slightly hazardous
		Fipronil (insecticide)	0.04 mg/kg	LD_{50} 92 mg/kg, moderately hazardous
		Fludioxonil (fungicide)	0.01–0.42 mg/kg	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
		Imidacloprid (insecticide)	0.49 mg/kg	LD_{50} 300–2000 mg/kg, moderately hazardous
		Myclobutanil (fungicide)	0.01–1.21 mg/kg	LD_{50} 1600 mg/kg, moderately hazardous
		Permethrin (insecticide)	0.35 mg/kg	LD_{50} 500 mg/kg, moderately hazardous
		Piperonyl butoxide (synergist)	0.05–12.46 mg/kg	LD_{50} > 7500 mg/kg, unlikely to present acute hazard
		Pyraclostrobin (fungicide)	0.40 mg/kg	LD_{50} > 500 mg/kg[iii]
		Spinosyn A and D (insecticide)	0.02 mg/kg	LD_{50} 3738 mg/kg, slightly hazardous
		Trifloxystrobin (fungicide)	0.08 mg/kg	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
8	Uruguay	Diazinon (insecticide)	0.03 mg/kg	LD_{50} 300 mg/kg, moderately hazardous
		Tebuconazole (fungicide)	0.19 mg/kg	LD_{50} 300–2000 mg/kg, moderately hazardous, possible carcinogen
		Teflubenzuron (insecticide)	0.11 mg/kg	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
20		Azoxystrobin (fungicide)	No levels given	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
		Bifenazate (acaricide)	No levels given	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
		Boscalid (fungicide)	No levels given	LD_{50} > 5000 mg/kg, unlikely to present acute hazard
		Carbaryl (insecticide)	No levels given	LD_{50} 300 mg/kg, moderately hazardous
		Carbendazim (fungicide)	No levels given	LD_{50} > 10000 mg/kg, unlikely to present acute hazard
		Clothianidin (insecticide)	No levels given	LD_{50} > 5000 mg/kg[i]
		Diazinon (insecticide)	No levels given	LD_{50} 300 mg/kg, moderately hazardous

(Continues)

TABLE 1 (Continued)

Reference	Country	Pesticide	Level detected	WHO oral toxicity in rats[11]
		Diuron (herbicide)	No levels given	LD$_{50}$ 3400 mg/kg, slightly hazardous
		Ethoprophos (insecticide)	No levels given	LD$_{50}$ 26 mg/kg (dermal), extremely hazardous
		Etoxazole (acaricide)	No levels given	LD$_{50}$ > 5000 mg/kg[iii]
		Fenpyroximate (acaricide)	No levels given	LD$_{50}$ 245 mg/kg, moderately hazardous, highly toxic by inhalation
		Imidacloprid (insecticide)	No levels given	LD$_{50}$ 300–2000 mg/kg, moderately hazardous
		Malathion (insecticide)	No levels given	LD$_{50}$ 2100 mg/kg, slightly hazardous
		Myclobutanil (fungicide)	No levels given	LD$_{50}$ 1600 mg/kg, moderately hazardous
		Permethrin (insecticide)	No levels given	LD$_{50}$ 500 mg/kg, moderately hazardous
		Piperonyl butoxide (synergist)	No levels given	LD$_{50}$ > 7500 mg/kg, unlikely to present acute hazard
		Propargite (acaricide)	No levels given	LD$_{50}$ 2200 mg/kg, slightly hazardous
		Propiconazole (fungicide)	No levels given	LD$_{50}$ 1520 mg/kg, moderately hazardous
		Pyraclostrobin (fungicide)	No levels given	LD$_{50}$ > 500 mg/kg[iii]
		Pyriproxyfen (insecticide)	No levels given	LD$_{50}$ > 5000 mg/kg, unlikely to present acute hazard
		Triflumizole (fungicide)	No levels given	LD$_{50}$ 695 mg/kg, moderately hazardous
		Trifloxystrobin (fungicide)	No levels given	LD$_{50}$ > 5000 mg/kg, unlikely to present acute hazard
		Triticonazole (fungicide)	No levels given	LD$_{50}$ > 2000 mg/kg, slightly hazardous
		Zoxamide (fungicide)	No levels given	LD$_{50}$ > 5000 mg/kg, unlikely to present acute hazard
37	Oregon (USA)	Bifenazate (acaricide)	0.15 mg/kg	LD$_{50}$ > 5000 mg/kg, unlikely to present acute hazard
		Bifenthrin (insecticide)	5.5 mg/kg	LD$_{50}$ 50–300 mg/kg, moderately hazardous
		Cypermethrin (insecticide)	1.23 mg/kg	LD$_{50}$ 250 mg/kg, moderately hazardous
		Piperonyl butoxide (synergist)	1.2–1.6 mg/kg	LD$_{50}$ > 7500 mg/kg, unlikely to present acute hazard
		Propiconazole (fungicide)	0.5 mg/kg	LD$_{50}$ 1250 mg/kg, moderately hazardous
27	Belgium	Abamectin (insecticide)	No levels given	LD$_{50}$ 300 mg/kg[iii]
		Bifenazate (acaricide)	No levels given	LD$_{50}$ > 5000 mg/kg, unlikely to present acute hazard
		Chlorfenvinphos (acaricide)	No levels given	LD$_{50}$ 31 mg/kg, highly hazardous
		Chlormequat chloride (plant growth regulator)	No levels given	LD$_{50}$ 670 mg/kg, moderately hazardous
		Chlorpyrifos (insecticide)	No levels given	LD$_{50}$ 135 mg/kg, moderately hazardous
		Dichlorvos (insecticide, not approved in EU)	No levels given	LD50 56 mg/kg, highly hazardous
		Dicrotophos (insecticide, not approved in EU)	No levels given	LD$_{50}$ 22 mg/kg, highly hazardous
		Dioxathion (acaricide)	No levels given	LD$_{50}$ 125 mg/kg, very toxic when inhaled[ii]
		Etoxazole (acaricide)	No levels given	LD$_{50}$ > 5000 mg/kg[iii]
		Imidacloprid (insecticide)	No levels given	LD$_{50}$ 300–2000 mg/kg, moderately hazardous
		Myclobutanil (fungicide)	No levels given	LD$_{50}$ 1600 mg/kg, moderately hazardous
		Propamocarb (fungicide)	No levels given	LD$_{50}$ 2000–5000 mg/kg, unlikely to present acute hazard
		Propiconazole (fungicide)	No levels given	LD$_{50}$ 1250 mg/kg, moderately hazardous
		Propoxur (insecticide)	No levels given	LD$_{50}$ 95 mg/kg, moderately hazardous

(Continues)

TABLE 1 (Continued)

Reference	Country	Pesticide	Level detected	WHO oral toxicity in rats[11]
		Tebufenpyrad (acaricide)	No levels given	LD$_{50}$ 595 mg/kg, moderately hazardous
		Triadimenol (fungicide)	No levels given	LD$_{50}$ 900 mg/kg, moderately hazardous

[a]Fishel FM. (2019). Pesticide Toxicity Profile: Neonicotinoid Pesticides. University of Florida IFAS Extension, PI-80, pp. 1–3. Available at: http://edis.ifas.ufl.edu/pdffiles/PI/PI11700.pdf (accessed 14 June 2019).
[b]Moffat A. (2011). Clarke's Analysis of Drugs & Poisons. London: Pharmaceutical Press.
[c]Rao KS. (2018). Toxicity of Pesticides. BEMS Rep. 4(2):31–36. Available at: https://www.bemsreports.org/sites/default/files/BEMSReports-4-2-31.pdf (accessed 17 May 2019).

plants are now grown indoors to ensure year round production and consistent THC levels. Moreover, pesticide concentrations in full-grown plants are higher than those found in younger plants due to them receiving more pesticide sprayings and pesticides accumulating in the plant.[27]

Table 1 displays data on pesticides found in cannabis samples from different countries. In one study, the levels of tebuconazole and bifenthrin were found to be within the LD$_{50}$ (median lethal dose) range.[28] Bifenthrin is a pyrethroid insecticide and classed as moderately hazardous by the World Health Organization (WHO). It is said to have relatively low toxicity to humans, however, when inhaled it can cause localized reactions in the respiratory tract such as shortness of breath, chest pain, coughing, and edemas. Some may experience an asthma-like attack that could prove fatal.[9] Tebuconazole is a triazole fungicide and classed as moderately hazardous by the WHO. Oral exposure has low toxicity, although when inhaled it can cause nose, lung, and throat irritation. The Enviromental Protection Agency (EPA) has classed it as a possible human carcinogen after observing liver tumors in mice when exposed orally to high doses of this pesticide.[29] Another study conducted in Belgium detected 19 pesticides including Dicrotophos, Chlorfenvinphos, and Dichlorvos. Additionally, Dicrotophos and Dichlorvos are not approved for use in the EU.[27]

As seen in Table 1, the levels of pesticides found in the different studies vary greatly. Many factors could influence the results such as pesticide dosage and application frequency. The herbal material analysed in these studies reported herein were seized by the police. It is not known how the growers had treated the plants.[27] Moreover, some studies do not actually give the quantity of pesticides found, only that they were detected. The pesticides found were mainly low and on the lower end of the World Health Organization's (WHO) toxicity classification. However, it must be stressed that these levels were found on unsmoked cannabis and the WHO toxicity levels are associated with oral toxicity in rats. These results should encourage future monitoring of pesticide residues in legal cannabis productions to evaluate safety for the consumers.

2.2 | Pyrolysis of pesticides in cannabis

When smoking cannabis with a cotton filter, users may be exposed to up to 30.1% of the pesticide residues from the original plant, whereas without a filter this could be as high as 69.5%.[30] Cannabis is typically smoked without a filter, therefore exposing the user to higher levels of dangerous compounds and their degradation products. Cannabis smoke contains many of the same carcinogens as tobacco smoke and reportedly four times as much tar as tobacco.[31] When inhaling smoke, it directly reaches the blood stream through the lung gas exchange, making bioavailability much higher than if the product was to be ingested, for example.[32] Additionally, cannabis smokers inhale two-thirds more per "puff" and retain the inhalation for longer than if they were to smoke a cigarette.[33] When smoked with a water pipe filter, the levels of pesticides found in the cannabis smoke (0.08–10.9% recovery) were similar to the levels found in tobacco smoke (2–16% recovery).[30] However, this study only addressed how much of the pesticide residues might reach the lungs, not the adverse effects that these levels could have on the user. This study also only used spiked material. A mixture of varying concentrations of pesticides were added to the leaf material. This method was optimized for the study of pesticides in smoke, although it may not be representative of what might be found in real samples, as the growers' application methods and quantities are unknown.[27]

Pesticide residues in cannabis will undergo pyrolysis and will be inhaled when smoked. Although it is yet unknown how harmful these chemicals are to humans when pyrolyzed and inhaled, the fact that up to 69.5% of residues are present in cannabis smoke should be of concern.[34] Moreover, a study looking at cannabis smoke alone found that it contained 20 times more ammonia than tobacco smoke and 3 to 5 times more hydrogen cyanide, nitric oxide, and aromatic amines than in tobacco.[35] The levels of toxicity while smoking cannabis containing pesticide residues could be compared to those of tobacco containing pesticide residues.[28] It has been shown that pyrothroid insecticides on tobacco transfer into the cigarette smoke. However, most of the residues were found within the cigarette's cotton filter.[36] Furthermore, there could be different pharmacokinetic interactions between the cannabinoids and the contaminants. For example, it has been shown that THC may have protective properties against the other harmful components found in cannabis smoke.[31]

Pyrolysis may transform some pesticides into more toxic forms that are then inhaled.[13] For example, the fungicide myclobutanil, has been found in cannabis samples in a number of studies and it is known to decompose into hydrogen cyanide when heated.[6,8,12,20,27,37] Hydrogen cyanide causes neurological, respiratory, cardiovascular, and thyroid problems and can also be lethal.[38] The World Health Organization have classified it as moderately hazardous. Myclobutanil

has been banned for use on cannabis in Oregon, but is allowed in Nevada in limited quantities.[24] Currently, there is a paucity of data concerning how other pesticides react when heated and what acute and chronic effects these would have on the user. More studies on cannabis smoke need to be conducted to better understand these effects. Currently, there are no reported cases in the literature of intoxication from pesticides or its metabolites due to smoking cannabis. However, there are several case reports of patients experiencing aspergillosis associated with smoking cannabis.[39]

3 | SAMPLING AND ANALYSIS

3.1 | Cannabis analytical methods

The main rationale for testing cannabis analytically is to confirm its identity as well as to test its potency. When analyzing cannabis, the total THC content is of most interest because this gives a potency indication.[40] Prior to instrumental analysis, herbal cannabis is preferably dried, pulverized, and sieved to ensure homogeneity. Gas chromatography (GC) and liquid chromatography (LC) coupled with mass spectrometry (MS) are the most common methods for analyzing cannabis and a broad range of cannabinoids. The best sensitivity is generally obtained through GC–MS or GC-FID (flame ionization detector), using low polarity stationary phases, as the main functional units of cannabinoids are phenolic. These are the methods recommended by the United Nations for the analysis of cannabis and cannabis products.[40] Although samples may need to be derivatized as the carboxylic acids degrade when placed into the injection port of the GC instrument. Silylation is commonly used as it imparts more volatility to the cannabinoids.[5] As cannabis is mainly tested for THC and other cannabinoids, potential harmful compounds are generally overlooked.

3.2 | Pesticide analytical methods

Over 700 pesticides are used routinely in the food industry and these foodstuffs are monitored for pesticide residues. GC–MS with electron impact (EI) or LC–MS/MS with electrospray ionization (ESI) are the most common techniques applied to multi-residue analysis of pesticides.[41] Multi-residue methods facilitate efficient monitoring as they allow the detection of up to a few hundred compounds per extraction and per analytical run.[42] The chemical nature of the pesticides to be detected dictates whether a LC or a GC approach should be used. A study that tested 500 different pesticides found that LC–MS/MS with ESI provided better sensitivity for all classes of pesticides except for the organochlorine pesticides, which were best analyzed by GC–MS.[41] LC–MS/MS is generally preferred over GC–MS as the tandem MS reduces matrix interferences. Liquid chromatography can also overcome issues associated with thermal instability. Another study used LC–MS for thermally labile and polar pesticides and GC–MS for volatile pesticides such as organophosphates and organochlorines.[43] The European Committee for Standardization has developed a method for determining the levels of pesticide residues in foods of plant origin. It has been validated for the extraction of 80 pesticides belonging to various chemical classes.[44] This method uses GC–MS and LC–MS/MS following acetonitrile extraction and dispersive solid phase extraction (dSPE) QuEChERS (quick, effective, cheap, easy, rugged, safe) clean-up.[45]

3.3 | Pesticide qualification and quantification in cannabis samples

The American Herbal Pharmacopoeia (AHP) compiled a list of 16 pesticides and three plant growth regulators (PGR) that are most likely to be used on cannabis.[25] However, this is not relevant to every country as these may vary from region to region, depending on product availability and on the different regulations on pesticides in each country. Pesticides will only be present in small quantities in cannabis samples, in comparison with the larger THC levels that will be detected. This is because pesticide levels decline after application due to photo oxidation, volatilization, and biological degradation. The quantities found are generally in μg/g or ng/g.[46] Cuypers et al. (2017) claim that pesticides will accumulate in cannabis plants due to receiving multiple sprayings over their lifetime.[27] The results from Table 1 show pesticide levels in the range of 0.01 to 800 mg/kg. The range in levels seen may be due in part to poor recovery with the analytical methods used. The percentage recoveries from some of the studies mentioned in Table 1 ranged from less than 50% to more than 120%, with the majority of recoveries falling between 70% and 120%.[6,8,28] Another main issue is that pesticides are numerous and belong to a broad spectrum of chemical classes. Moreover, pesticides from completely different classes can be found in the same cannabis sample. They may be acidic, basic, or neutral, varying in polarity and solubility. Some are thermally labile, while others may easily bind onto surfaces.[46]

Table 2 illustrates the analytical techniques used that successfully detected pesticides in cannabis. Not all studies quantified the pesticides found. It is important to note that these studies used a mixture of spiked material and seized plants. Therefore, some studies looked at what truly is in the samples, whereas others tested their analytical methods. The limits of quantification (LOQ) were only given for three of the studies that used LC–MS/MS. In a study conducted by Alder et al. in 2006, 500 pesticide residues were analyzed by GC–MS and LC–MS/MS. It was determined that LC–MS/MS was a much more sensitive method due to the LOQs being much lower.[41]

3.3.1 | Sample preparation

Cannabis is a highly complex matrix. Not only does it contain many cannabinoids but also many secondary cannabinoids and terpenoids. If pesticides are to be detected and quantified in cannabis samples accurately, a representative sample must be collected, homogenized,

TABLE 2 Methods that have successfully detected pesticides in cannabis samples

Reference	Analytical technique	Clean up/extraction	Pesticides detected	LOQ GC–MS	LOQ LC–MS/MS
27	LC–MS/MS	dSPE cleanup and EN15662 QuEChERS	Abamectin Bifenazate Chlorfenvinphos Chlormequat chloride Chlorpyrifos Dichlorvos Dicrotophos Dioxathion Etoxazole Imidacloprid Myclobutanil O-Phenylphenol Propamocarb Propiconazole Propoxur Tebufenpyrad Triadimenol	None given	None given
28	UPLC/MS–MS and GC–MS	EN15662 QuEChERS	Bifenthrin DMST Hexythiazox Imidacloprid Propamocarb Propiconazole Tebuconazole	None given	None given
6	LC–MS/MS with electrospray ionization	dSPE cleanup and modified QuEChERS	Boscalid Dinotefuran Diuron Fipronil Fludioxonil Imidacloprid Myclobutanil Permethrin Piperonyl butoxide Pyraclostrobin Spinosyn A Spinosyn D Trifloxystrobin	None given	Range from 0.02 mg/kg to 0.5 mg/kg
20	LC–MS/MS	AOAC 2007.01 acetate buffered QuEChERS	Azoxystrobin Bifenazate Boscalid Carbaryl Carbendazim Clothianidin Diazinon Diuron Ethoprophos Etoxazole Fenpyroximate Imidacloprid Malathion Myclobutanil Permethrin Piperonyl butoxide Propargite Propiconazole Pyraclostrobin Pyriproxyfen Triflumizole Trifloxystrobin	None given	None given

(Continues)

TABLE 2 (Continued)

Reference	Analytical technique	Clean up/extraction	Pesticides detected	LOQ GC-MS	LOQ LC-MS/MS
			Triticonazole Zoxamide		
8	LC–MS/MS	EN15662 QuEChERS, acetate buffered QuEChERS and modified citrate buffered QuEChERS	Diazinon Tebuconazole Teflubenzuron	None given	0.01 mg/kg 0.05 mg/kg 0.05 mg/kg
12	GC–MS and LC–MS/MS	SPE clean-up and AOAC 2007.01 acetate buffered QuEChERS	Azadirachtin Bifenthrin Dichlorvos Imidacloprid Myclobutanil	None given	None given
37	LC–MS/MS	dSPE cleanup and EN15662 QuEChERS	Bifenazate Bifenthrin Cypermethrin Piperonyl butoxide Propiconazole	None given	0.025 mg/kg 0.025 mg/kg 0.39 mg/kg 0.097 mg/kg 0.195 mg/kg

extracted with suitable solvents, and interferences removed. The lower the target analyte concentration the more robust the clean-up needs to be.[34]

Pesticides must be extracted from the sample matrix and isolated from any interfering materials for successful and accurate analysis. Cannabinoids are found in the glandular trichomes on the leaves and flowers which are highly resinous. Many pesticides are hydrophobic, therefore they adhere to these structures, making them hard to isolate from the matrix.[46] Moreover, cannabinoids and terpenes are hydrophobic and they are readily extractable by organic solvents, such as acetonitrile. This is why the European standard method (EN15662) uses citrate buffered QuEChERS as it does not co-extract the cannabinoids when trying to isolate the pesticides.[8] The EN15662 method is recommended for the analysis of pesticides in foods of plant origin. It is not specifically recommended for pesticide analysis in cannabis, however, it has been modified and used for this purpose.[8,28] This involves drying out the sample, coarsely grinding the herbal material for homogenization, an acetonitrile extraction, and QuEChERS dispersive SPE clean-up. The first step is the extraction that uses an organic solvent and salt solution (usually $MgSO_4$). The second step is dispersive SPE which further extracts and cleans the supernatant from the previous step. The purpose of this is to remove sugars, lipids, organic acids, sterols, proteins, pigments, and excess water.[47] Lozano et al.[48] proposed using calcium chloride instead of magnesium sulfate (employed in the EN 15662 method) for the clean-up step as it reduced matrix effects and improved recovery, however, this was only validated for tea samples.

The most universal extraction method is liquid–liquid extraction (LLE). However, this method is unsuitable for many analyses as is consumes a large amount of solvent as well as being a laborious method.[49] One study used headspace solid-phase micro extraction (SPME) of pesticide residues from cannabis samples. This method provides a simpler and more rapid quality control of plant material.[49] Unfortunately, this method is preferably coupled with GC–MS, which cannot analyze all types of pesticides.[50]

EDGE® is a new system for extracting pesticides from cannabis. It includes a dispersive SPE clean-up phase in the same one sample cell. It offers the fastest automated pesticide extraction. It has been tested and efficiently extracted over 400 pesticides from cannabis in under 7 minutes. Recoveries were between 80% and 115% for analysis with GC–MS and between 81% and 117% for analysis with LC–MS.[51]

3.3.2 | GC-MS

GC–MS is perceived to be the reference method for the identification and confirmation of pesticides in different materials. Libraries containing reference spectra for many pesticides as well as their metabolites and decomposition products are designed for use with GC–MS.[9] Sample preparation for GC–MS is usually SPME or QuEChERS. These samples can be directly injected in splitless mode and ionized using electron impact ionization (EI). GC–MS is a selective and sensitive method for volatile and hydrophobic pesticides such as organophosphates and organochlorines. However, GC–MS can be a source of pesticide artifacts and decomposition products due to light sensitivity, oxidation, hydrolysis, and heat. Lack of volatility or thermal lability could be overcome with derivatization, however, it is not known in advance what a cannabis sample will contain and therefore it is problematic to know which derivatizing agent to use. Additionally, derivatizing would only add to the sample preparation time as well as complicating the sample matrices.[52] This is why many recent studies have used LC–MS/MS as it can reduce matrix interferences and overcome issues with thermally labile and highly polar pesticides as well as pesticides with high molecular weights.[43]

3.3.3 | LC-MS/MS

Historically, LC was used more rarely in the past because traditional detectors associated with this technique, such as UV, diode array, and

fluorescence were less selective and less sensitive than the detectors used with GC instruments.[41] However, in the past couple of decades, the development of atmospheric pressure ionization (APCI) and electron spray ionization (ESI) coupled with MS have largely increased the sensitivity of LC detection.[41] LC–MS/MS is preferred for ionic and polar pesticides. This is a much more versatile and universal technique compared with GC–MS, however, organochlorine pesticides are notoriously difficult to ionize with ESI.[53] Some chlorinated pesticides have been ionized with atmospheric pressure chemical ionization (APCI) and analyzed with LC–MS to overcome the issues faced with ESI.[52] QuEChERS sample preparation can also be used for LC–MS/MS. However, this can be made more straight forward for analysis with LC–MS/MS by using LLE with acetonitrile as it requires fewer steps and is just as effective.[52]

3.3.4 | Other methods

Supercritical fluid chromatography (SFC) offers high resolution. This method was used in a study that was able to rapidly and simultaneously detect pesticides over a wide range of polarities and molecular weights, including highly hydrophilic ones.[54] SFC eliminates the need for two different analytical instruments to analyze a single sample. The biggest drawback, however, is that the run times are short which may result in the presence of isobaric interferences, therefore reducing the method's resolution.[52] LC-UV has been used successfully for the quantification of paraquat in cannabis. This is an easy method to perform, however, it is not suitable for multiresidue analysis. A study using capillary electrophoresis-UV detected three herbicides in cannabis.[55] This is a simple and fast separation method for highly polar pesticides that provides good resolution and recovery. Unfortunately, the LOQs (paraquat: 5 μg/g, glyphosate: 10 μg/g, AMPA: 10 μg/g) are deemed to be too high for the regulatory action limits.[55] For example, current LOQs for various pesticides in the state of Oregon lie between 0.00025 and 0.005 μg/g. Regulatory action limits lie between 0.1 and 2 μg/g. Similar values can be found for different states.[56]

3.4 | Towards developing standardized testing

Due to the disparity of the legal status of cannabis worldwide, it is difficult to establish botanical and chemical quality standards for such materials.[8] Cannabis standards of common strains would be needed for efficient testing as the different properties from the different strains could alter results from pesticide analysis due to ion enhancement or ion suppression.[57] It cannot be ignored that standardized testing should be considered as becoming mandatory in countries where the drug is already legal. If implemented, this testing will also assist other countries that are planning on or are in the process of legalizing cannabis.

Due to the wide variety of physical properties of the pesticide components and the complexity of the cannabis matrix, developing a standardized method is proving complicated and involves numerous stages, particularly for sample preparation. Using both GC–MS and LC–MS provides complementary analysis to cover the different polarity and thermal needs of the different pesticides. Integration of these two systems into a MS database would be extremely useful for laboratory testing so as to cover a wide scope of pesticides.[52] However, these two analytical systems are expensive and analysis can be extensive due to instrument parameter modifications. Moreover, the regulatory requirements for pesticide testing vary between countries and vary from state to state in the USA, which in turn influences the sample preparation, instrumentation, and techniques performed.[53]

4 | SUMMARY

It is apparent that pesticide use on cannabis crops is ubiquitous. Appropriate residue levels on legal cannabis plantations need to be determined and quality controls implemented. Further research is required to assess how these pesticides affect the human body when pyrolyzed, as there is a paucity of data in this area. Knowing to what extent the consumer may inhale pesticide residues from smoking cannabis is also essential. To date there is only one comprehensive study conducted by Sullivan et al.[30] that aimed to bridge the gap between detected pesticide residue levels and internal pesticide doses. Further toxicity studies are therefore required to assess fully the fate and behavior of pesticide materials on cannabis.

Numerous pesticides of different classes have been detected in cannabis materials. When quantification has been achieved, levels range from 0.01 to 800 μg/g, although the concentrations are generally found in the low μg/g region. The majority of these detected pesticides are classed as moderately hazardous. The analytical methods chiefly employed for this analysis are currently QuEChERS extraction with GC–MS or LC–MS/MS.

The determination of pesticides in cannabis samples is not targeted by routine instrumental analysis. A few studies have successfully detected pesticide residues on cannabis. However, additional work is needed to further develop rigorous methods that satisfy the requirements for all analytes of interest. The development of these analytical techniques is challenging due to many factors such as cannabis matrix complexity, contaminants at trace-levels, the simultaneous detection of multiple chemically variable contaminants, and contrasting laws. In countries where medical and recreational cannabis is legalized, work towards pursuing a standardized protocol for pesticide detection, using standard cannabis reference materials, should be considered.

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