A RESPONSE TO CALIFORNIA'S PROPOSED TESTING REQUIREMENTS

Commissioned by CannaCraft Inc., care of Nick Caston
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SUMMARY

The following is a summary of Project CBD's concerns with the State of California's proposed regulations for cannabis testing regarding solvents (§5310), pesticides (§5313), and heavy metals (§5328), and recommendations for amending them. The primary goal of this statement is to describe the methodological and technical errors in the Bureau of Marijuana Control's *Initial Statement of Reasons*, and to provide corrections and revisions to these errors [1, 2]. These regulations can and should be adjusted as more toxicological data is made available. We feel that much safety information is lacking, particularly with respect to vaporizing and smoking pesticides. We believe the following recommendations will benefit patients, recreational users, and people working in the industry.

SOLVENTS

California's proposed regulations for solvents are problematic because:

- The safety data from California Department of Industrial Relations' California Division of Occupational Safety and Health (Cal/OSHA) and from the National Institute for Occupational Safety and Health (NIOSH) have been misinterpreted.
- At times, data referenced in the State's document have been incorrectly transcribed from Cal/OSHA and the U.S. Pharmacopeia (USP).
- §5310 allows for the use of highly dangerous solvents, including benzene, which are not necessary for cannabis manufacturing and should not be allowed under any circumstances.

We recommend the following amendments to the solvent regulations:

- In Table 1 we have proposed revised action limits for solvents in both inhaled and ingested cannabis products, based primarily on Cal/OSHA's short-term exposure limits (STEL) and the USP's pharmaceutical safety guidelines.
- Because cannabis extracts can be safely made with Class 3 solvents like ethanol and butane, we recommend banning the use of Class 1 solvents as unnecessary and unsafe.
- We further recommend that regulators work with product-makers to determine if Class 2 solvents are necessary for extracting cannabinoids. If not, they should be banned for use in manufacturing extracts.

PESTICIDES

California's proposed regulations for pesticides are problematic because:

- No references are given from which the proposed limits on pesticides in ingested products were determined.
- In §5313 it is assumed that individuals ingest up to 10% of their body weight in edibles each day. This is not only absurd, but it contradicts the assumption in §5310 that people ingest no more than 10 grams per day.
- Limits on pesticides in smoked products are ultimately based on the assumption that 0.1 ppm of any pesticide is safer than cigarette smoke. Setting safety limits based on the safety of cigarettes is nonsensical. Tobacco's poor regulatory standards should not be used as a model for the cannabis industry.
- The limits of detection (LODs) of Category 1 pesticides on cannabis products have not been validated.
- The safety of ingested pesticides are evaluated based on the reference dose (RfD). The acceptable daily intake (ADI) is a more appropriate measure, as it accounts for chronic ingestion (e.g. food or medicine) whereas the RfD does not.

We recommend the following amendments to the pesticide regulations:

- Pesticides should be separated into three categories, as shown in Table 3. Category 3 pesticides are allowed for use on cannabis, will be tested in each batch, and the action limits are set based on health or environmental concerns. Category 2 pesticides are banned for use on cannabis but are common. Every batch will be tested for Category 2 pesticides and the action limits are set at the pesticides' limits of detection. Category 1 pesticides are banned for use on cannabis, but are uncommon and will not be tested in every batch.
- Action limits for Category 1/2 pesticides should be set at the limit of detection (LOD) for the given pesticides. Regulators should work with labs in California to determine current LODs for different pesticides in different cannabis products, including concentrates, flower, and edibles.
- The expected daily consumption of edibles should be set to a reasonable value, such as 10 g or 250 mg/kg, in the calculation of action limits for ingested products.
- In Table 2 we have proposed action limits for pesticides in ingested cannabis products, based on the ADIs tabulated by the European Food Safety Administration (EFSA) and the World Health Organization (WHO).
- Regulators should determine a standard method for estimating safe levels of acutely inhaled pesticides based on oral safety data by working with safety organizations and toxicologists.

OTHER REGULATIONS

Certain changes to the lab regulations are dependent on changes to manufacturing and growing regulations. To be consistent with the recommendations herein, we recommend that:

- The manufacturing regulations ban the use of certain solvents in cannabis manufacturing, including all Class 1 solvents.
- The growing regulations include a stipulation allowing on-site testing for heavy metals.
- If these recommendations are taken, then testing for metals and Category 1 pesticides will not be required on every batch, as stipulated under the current proposal. Testing grow sites should be sufficient to ensure the absence of heavy metals. Similarly, systematic or random product testing for banned pesticides would be sufficient to ensure the absence of Category 1 pesticides. This would significantly reduce the cost of testing.

Table 1. Revised action limits we propose for solvents on inhaled and ingested cannabis products measured in parts per million (µg/g).

Solvent	Action limit for inhaled products (µg/g)	Action limit for ingested products (µg/g)
Acetone	1780	5000
Acetonitrile	105	410
Butane	1900	5000
Chloroform	9.78	60
Ethanol	1900	---
Ethyl acetate	1400	5000
Ethyl ether	1500	5000
Ethylene oxide	9.83	10
Heptane	2000	5000
Hexane	180	290
Isopropyl alcohol	1225	5000
Methanol	325	3000
Methylene chloride	435	600
Naphtha	1800	4500
Pentane	1800	5000
Propane	1800	5000
Trichloroethylene	80	80
Toluene	560	890
Xylene (all isoforms)	655	2170

Table 2. Revised action limits we propose for pesticides in ingested cannabis products.

Pesticide	Action limit for ingested products (µg/g)
Acequinocyl	2.3
Bifenazate	1
Captan	5
Clofentezine	2
Cypermethrin	0.16
Etoxazole	5
Fenhexamid	5
Fenpyroximate	1
Flonicamid	2.5
Hexythiazox	3
Kresoxim-methyl	5
Oxamyl	0.1
Pentachloronitrobenzene (Quintozene)	1
Permethrin	5
Phosmet	1
Piperonyl butoxide	20
Pyrethrins	4
Pyridaben	1
Spinetoram	2.5
Spinosad	2
Spiromesifen	3
Spirotetramat	5
Trifloxystrobin	4

Table 3. List of pesticides and their categorization. Category 1 and 2 pesticides are banned from use on cannabis. Action limits are set at the limits of detection for banned pesticides. Category 2 and 3 pesticides should be tested in each batch.

Pesticide	Category	Pesticide	Category
Abamectin	2	Glyphosate	1
Acephate	1	Hexythiazox	3
Acequinocyl	3	Imazalil	1
Acetamiprid	1	Imidacloprid	2
Aldicarb	1	Kresoxim-methyl	3
Azoxystrobin	1	Malathion	2
Bifenazate	3	Metalaxyl	2
Bifenthrin	2	Methiocarb	1
Boscalid	1	Methomyl	1
Captan	3	Methyl parathion	1
Carbaryl	2	Mevinphos	1
Carbofuran	1	Myclobutanil	2
Chlorantraniliprole	1	Naled	1
Chlordane	1	Oxamyl	3
Chlorfenapyr	1	Paclobutrazol	2
Chlorpyrifos	1	Pentachloronitrobenzene (Quintozene)	3
Clofentezine	3	Permethrin	3
Coumaphos	1	Phosmet	3
Cyfluthrin	2	Piperonal butoxide	3
Cypermethrin	3	Prallethrin	1
Daminozide	2	Propiconazole	1
DDVP (Dichlorvos)	2	Propoxur	1
Diazinon	1	Pyrethrins	3
Dimethoate	1	Pyridaben	3
Dimethomorph	1	Spinetoram	3
Ethoprop(hos)	1	Spinosad	3
Etofenprox	1	Spiromesifen	3
Etoxazole	3	Spirotetramat	3
Fenhexamid	3	Spiroxamine	1
Fenoxycarb	1	Tebuconazole	2
Fenpyroximate	3	Thiacloprid	1
Fipronil	1	Thiamethoxam	1
Flonicamid	3	Trifloxystrobin	3
Fludioxonil	1		

Introduction

This document is a response to the Bureau of Marijuana Control's proposed regulations for testing laboratories. Project CBD specifically reviewed sections 5310 and 5313, which describe the allowable limits for solvents and pesticides in cannabis products. Our objective is to participate constructively in the legislative process to ensure sensible testing regulations that protect public safety. In particular, we've sought to address errors and faulty assumptions that lead to irrelevant action limits.

At the very least, this report should indicate the *relative* safety of solvents and pesticides, if not the absolute limit, based on currently available data published by public health organizations. Regrettably, there is very little data on the safety and hazards of inhaling pesticides.

Due to the short period for commenting, we were not able to address discrepancies in regulations between different U.S. states, nor are we able to extend our suggestions to limits for different types of products, including oral-mucosal tinctures and topicals.

General procedure to determine action limits

Acceptable exposure to contaminants on cannabis depends on how cannabis is administered. Vaporization, ingestion, smoking, oral-mucosal (e.g. sublingual), and topical application all have different safety profiles. Ingestion of contaminants is typically less harmful due to protective mechanisms of the digestive system. In contrast, vaporization, oral-mucosal administration, and smoking all allow adulterants to be absorbed directly into the bloodstream, so products consumed in these ways will generally require more stringent action limits.

Smoking creates the added complication of potential pyrolysis products. For example, pesticides with nitrile groups (e.g. myclobutanil, cypermethrin) can decompose to cyanide when burned.* Polycyclic aromatic hydrocarbons and triazoles are also common pyrolysis products. (The former are potent carcinogens, while the latter are not well studied.) The safety of topicals depends on the contaminant. Some chemicals permeate the skin easily, while others do not [4].

At some point soon, we hope to see the regulations updated to account for these differences.

Safe ingestion limits for contaminants are tabulated as Acceptable Daily Intake values (ADI, also known as Tolerable Daily Intake or TDI). ADI values are determined with the expectation of daily consumption over the course of a lifetime. An appropriate action limit for contaminants on ingested cannabis products can then be determined using the contaminant's ADI and an upper bound on daily cannabis use. This equation is derived in Appendix A: Equations Relating Regulatory Limits to Safety.

Safe concentrations of inhaled solvents are tabulated by the California Department of Industrial

* The creation of cyanide as a pyrolysis product, although it sounds scary, is unlikely to cause harm: even assuming the 100% conversion to cyanide, pesticides produce 10-20 times less cyanide by weight than the amount of the pesticide. Since adverse effects from cyanide are minimal for brief exposure at concentrations below 20 mg/m^3 [3], this would require 200-400 ppm of a pesticide on cannabis, assuming full conversion to cyanide. At this level, the pesticide would likely cause much greater toxicity.

Relations' California Division of Occupational Safety and Health (Cal/OSHA) as Short-Term Exposure Limits (STELs) [5]. The STEL for a compound is considered to be the maximal safe concentration of a chemical that someone is exposed to for less than 15 minutes. To determine an action limit for inhaled cannabis products, one needs to take into account the contaminant's STEL, as well as the maximum amount of cannabis likely to be inhaled acutely and the minimum lung volume of an individual. This equation is also derived in Appendix A.

If no STEL has been provided for a chemical, then we used the Permissible Exposure Limit (PEL) as the maximum allowable lung concentration. The PEL of a compound is considered to be the maximal safe ambient concentration of a chemical for an 8-hour workday. It is always more stringent than the STEL.

§5310: SOLVENTS

All of the data regarding solvents discussed below, as well as a comparison between our proposed limits and §5310(c), are provided in tables 4 and 5 of Appendix C: Solvent Safety Data and Limits.

Our proposed revisions to the action limits for solvents on inhaled and ingested cannabis products are given in Table 1. These are dependent, in part, on the manufacturing guidelines for cannabis, which may ban the use of certain solvents in the processing of cannabis. High-quality cannabis extracts and concentrates can be safely made with Class 3 solvents, the safest category of solvents.

We propose the removal of benzene and 1,2-dichloroethane from §5310(c) altogether. These are Class 1 solvents, which according to the FDA "should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect" [6]. We recommend that these solvents be banned from use for processing cannabis; it is not necessary to expose medical patients or recreational users to these dangerous chemicals.

Class 2 solvents such as chloroform and methanol are listed in Table 1 with revised action limits. Given that cannabis extracts can be made using Class 3 solvents, however, regulators should reconsider whether these solvents are appropriate for use in cannabis manufacturing.

We have further proposed removing petroleum ether from the list of permissible solvents. According to the FDA, "no adequate toxicological data" has been determined for petroleum ether [6]. It is unreasonable to set an arbitrary limit of exposure when it is not necessary to use this chemical in cannabis processing.

REVISING LIMITS ON INHALED PRODUCTS

The regulatory limit on inhaled products should be such that the STELs of solvents are not exceeded when someone vaporizes cannabis extracts. In cases where the STEL has not been determined by Cal/OSHA, we utilized the STEL determined by NIOSH [5,7]. If the STEL is given in units of mg/m^3, then this value is used to determine the action limit for cannabis (see Appendix A). If neither agency has documented a STEL for a solvent, then the PEL from Cal/OSHA was used as the maximal lung concentration.

Of the 19 solvents which California proposes regulating (excluding benzene, 1,2-dichloroethane, and petroleum ether), the limits for 9 are determined from the STELs reported in mg/m^3 by Cal/OSHA [5]. The STEL for ethylene oxide is only given in units of parts per million by volume (ppmv), so this is converted to parts per million by weight (μg/g or ppmw) as described in Appendix A. No STEL is provided for pentane or naphtha, so we used the STELs determined by NIOSH [8,9].

The STELs have not been determined for the remaining solvents (butane, chloroform, ethanol, ethyl acetate, hexane, propane, and trichloroethylene). We consequently used the more stringent PEL values from Cal/OSHA for all but trichloroethylene. Trichloroethylene had a lower calculated ingestion action limit than the inhalation action limit. In light of the hazards of this chemical, the lower value was used to set both the limit on ingestion and inhalation.

ISSUES IN §5310(C): INHALED PRODUCTS

There are currently a number of errors in the calculation of California's proposed solvent action limits (§5310) [1,2]. The proposed methodology in §5310 is similar to our method as described above[†]. This process, however, was not actually followed in the creation of §5310's proposed action limits.

Specifically: The limits on residual solvents in §5310 incorrectly report safety data from Cal/OSHA. The STEL for inhaled solvents is reported in units of mg/m^3 or parts per million by ***volume*** (ppmv; sometimes written ppm). But the limits for solvents in cannabis products are determined as parts per million by ***weight*** (ppmw or μg/g; also sometimes written ppm). Ppmw and ppmv are not the same. The conversions between relevant ppmw, mg/m^3, and ppmv are given in Appendix A.

As well, the action limits proposed in §5310 do not always match the referenced limits. The limits for benzene, naphtha, pentane, petroleum ether, propane, and trichloroethylene are either not given in the referenced document, or the value does not match the regulations [5].

The action limit for benzene is determined in part by the USP limit for ingestion, but this not make sense because it compares two different units (ppmv in Cal/OSHA, ppmw in USP) [10]. The same issue occurs with the limit on trichloroethane. For naphtha, it appears that the units of mg/m^3 and ppmv were confused, as the PEL in mg/m^3 is used without explanation. Moreover, a STEL for naphtha is in fact provided by NIOSH, so — per the stated methodology — this value should be used instead of the PEL reported by Cal/OSHA.

The STEL for pentane is also given by NIOSH (610 ppmv, 1800 mg/m^3) but not by Cal/OSHA. An action limit of 750 ppm for pentane is suggested based on ACGIH's limit; the discrepancy between NIOSH's and ACGIH's limits is not addressed.

No STEL has been determined for propane, but the PEL is 1800 mg/m^3 or 1000 ppmv. A limit of 2100 ppm is suggested, which is NIOSH's level for "immediately dangerous to life or health" [11]. It is unclear why the PEL is not used here; allowing concentrations that cause an immediate danger to life is clearly irresponsible.

[†] First, Cal/OSHA is checked for STELs, then NIOSH and the American Conference of Governmental Industrial Hygienists (ACGIH) are checked for STELs. If no STEL is available for a solvent, the PEL is used. Unlike our method, §5310 simply used the STEL in ppmv as the action limit.

Because petroleum ether is a mix of hydrocarbons, it is difficult to determine a limit. The proposed 400 ppm action limit in §5310(c) was based on naphtha simply because they are similar compounds.

Revising limits on ingested products

To set limits for solvents on products meant for ingestion, we use the acceptable daily intake values for solvent tabulated by the USP [10]. These action limits (reported as ppmw) are based on an assumed consumption of 10 g/day, which we believe is reasonable for cannabis edibles. Class 1 solvents (benzene and 1,2-dichloroethane) are highly dangerous and should not be used in the making of any cannabis products. Class 3 solvents are much less dangerous, with an acceptable daily intake of 50 mg/day.

Ethanol has been removed from the list. Sativex®, an oral-mucosal preparation of THC and CBD dissolved in ethanol, contains 50% ethanol by volume. Sativex® has been approved in many countries internationally, and is in Phase III clinical trials in the US. As long as pharmaceutical-grade ethanol is used, up to 0.2 g ethanol should not be problematic for ingestion [12]. Products dissolved in ethanol must be clearly labeled with the amount of ethanol per serving, as they could be problematic for individuals with liver disease or alcoholism.

Three solvents were not listed by the USP: propane, butane, and naphtha. According to the US Occupational Safety and Health Administration (OSHA), butane "is affirmed as generally recognized as safe as a direct human food ingredient," similar to a Class 3 solvent. Based on this, we set the action limit for butane at 5000 ppmw [13]. The FDA has also determined propane to be generally recognized as safe (GRAS), so we also set its action limit to 5000 ppmw [6].

Naphtha is a mix of hydrocarbons. No ADI for naphtha has been determined. With other hydrocarbons, the mean ratio of inhalation to ingestion limits is 0.4 to 1. Applying this to naphtha indicates that 4500 ppmw is an appropriate action limit for ingested products.

Issues in §5310(c): ingested products

Most limits were taken from values tabulated by USP, which are given in ppmw, so the units do not need to be corrected as they were for inhalation. By using the USP action limits without adjustment, regulators implicitly assume that the maximum amount of edibles consumed per day is 10 g; this conflicts with the assumption that individuals ingest up to 10% of their bodyweight in edibles per day, as stated in §5313. This will be addressed in comments on the pesticide action limits. Ten grams per day is reasonable for individuals using less than 30-50 mg of THC per day, as described in Appendix B. Some patients use upwards of 500 mg of cannabinoids, which speaks to the importance of allowing concentrates and regulating them using separate limits.

§5310 states that the USP has not determined limits for ethylene oxide and isopropyl alcohol, however isopropyl alcohol (2-propanol) is listed as a Class 3 solvent with a limit of 5000 ppmw, and the limit for ethylene oxide is stated to be 10 μg/g (10 ppmw) [10].

It is suggested that since propane and butane are similar to pentane (these are 3-, 4-, and 5-C unsaturated hydrocarbons, respectively), the same limit should be used. But this is a misunderstanding of chemistry. Pentane and hexane are also structurally very similar (5- vs. 6-C hydrocarbons) yet require quite different limits (5000 vs. 290 ppmw)[‡]. That said, both butane and propane are GRAS, so a 5000 ppmw limit should be appropriate. The action limit for naphtha is set at the inhalation limit given by ACGIH. It does not make sense to simply use an inhalation limit as a limit for ingestion. No explanation is provided as to why the PEL for naphtha is used as the ingestion limit in §5310(c); it appears to be a mistake.

PESTICIDES

CATEGORIZATION OF PESTICIDES

§5313 describes California's proposed regulations on pesticides. These are broken into two categories. Category 1 pesticides are considered either highly toxic, dangerous to the environment, or poorly understood, and hence are banned from use on cannabis. If these exceed the limit of detection (LOD) then the batch fails. This categorization is useful. A more appropriate regulation would be to introduce a third category. Category 3 would consist of all the pesticides listed as Category 2 in §5313(b), which are the pesticides allowed for use on cannabis [2]. Category 1/2 pesticides would both be banned from use on cannabis, but Category 2 would consist of commonly used pesticides, such as myclobutanil, paclobutrazol. Each batch would be tested for Category 2/3 pesticides.

Category 1 pesticides, the banned pesticides that are uncommon, would only be checked in random or systematic product tests. Random product testing would look for pesticides in any of the three categories. Any product which fails a random product test will be more closely monitored for a period after failing, and will have to cover the cost of regularly testing for all regulated pesticides. This separation would greatly reduce the cost of testing, while still ensuring that commonly used pesticides are not in cannabis products. The list of Category 1 and Category 2 pesticides will occasionally need to be updated to match trends in pesticide use. An alternative to random product testing is to test Category 1 pesticides systematically (e.g. on every 50th batch).

From this point on, any mention of categories of pesticides will refer to the classification in Table 3.

GENERAL ISSUES WITH §5313(B), CA'S PESTICIDE ACTION LIMITS

The action limits for Category 1/2 pesticides may be lower than the current LOD for cannabis testing labs. The detection of low levels of pesticides has not been validated in cannabis matrices. The quantification of pesticide residues needs to be validated for each different kind of product that will be tested: raw flower, concentrated oil, oil dissolved in ethanol, different kinds of edibles, etc. Some labs have internally validated and optimized equipment for the detection of pesticides, but no standard methodology has been determined. Table 2 only provides limits for the Category 3 pesticides indicated in §5313 of [2], since we are uncertain of the current LODs for Category 1/2 pesticides.

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‡ Hexane is particularly toxic because it is metabolized by the body into a potent neurotoxin, 2,5-hexanediol.

Although §5313 states a method by which action limits for Category 3 pesticides are determined, no references are provided for the data used to calculate ingestion action limits. With respect to inhalation, regulations on tobacco were used as a model. This is a poor choice: tobacco is loosely regulated because the end product is understood to be toxic with or without pesticides (and because of lobbying from the tobacco industry[§]). As such, this response does not attempt to strictly follow the methods of §5313.

INHALATION OF PESTICIDES

Based on the pesticide safety data available, we do not feel comfortable recommending action limits for pesticides on inhaled products. Instead, we explain the type of data that could be used to determine action limits.

To determine a safe limit of pesticide on inhaled products, it is necessary to consider whether the product is vaporized or smoked. Burning pesticides will cause partial degradation (called pyrolysis), which produces smaller molecules. These smaller molecules may be more or less toxic, and are more likely to enter the bloodstream immediately, since large particulates are difficult to absorb through the lungs.

As a first estimate, we assume that 100% of the pesticide remains intact. In the future, pyrolysis studies should be performed on common pesticides so as to determine the profile of toxins that enter the lungs when contaminated cannabis is smoked.

Pyrolysis is less likely to occur when vaporizing cannabis for two reasons. First, vaporization occurs at a lower temperature than burning, so less energy is available to cause a reaction. Second, when chemicals vaporize, they form a small droplet (an aerosol or particulate) consisting of the pesticide along with cannabinoids, terpenes, and other compounds. Pyrolysis involves a radical mechanism, but cannabinoids are chemical antioxidants that may inhibit this radical reaction. As such, we suspect that vaporization will deliver a larger amount of pesticides to the lungs than smoking. Again, this should be studied further.

Ideally, safe levels of inhaled pesticides would be tabulated for brief exposure (10-15 minutes) similar to STELs for solvents. But most investigations only study oral and dermal exposure. A safety parameter determined from this type of study is the no-observable-adverse-effect level (NOAEL). However, there are many different NOAELs: for acute ingestion, 30-day ingestion, ingestion for multiple months to years, acute and chronic dermal application, etc. These experiments are performed on male and female animals from many different species. And there are different NOAELs corresponding to different endpoints, such as toxicity, carcinogenicity, and developmental harms. We are not toxicologists, and do not feel capable of interpreting these data to determine appropriate action limits for inhaled cannabis products.

If the oral bioavailability of a pesticide is known, then one can set a limit on safe inhalation levels using the NOAEL for chronic ingestion, adjusting the parameters with the assumption of 100% bioavailability

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[§] The tobacco industry spends close to $20,000,000 lobbying the U.S. government each year. [14]

when absorbed through the lungs**. This is inevitably an overestimate, which is preferable to underestimating the potential hazard.

Different matrices and modes of administration (e.g. smoking a joint vs. using a bong vs. dabbing) will lead to different particulate sizes and levels of pyrolysis products. Particulate size can affect absorption: small particulates are absorbed directly through the lungs, while large particulates are coughed up and ingested. Only one published study to date has looked at the delivery of pesticides when smoking contaminated cannabis [16]. They found that up to 70% of the pesticides remained intact in the smoke, but this greatly depended on the device used to smoke.

Issues in §5313(b): Inhaled Products

As stated in §5313, the EPA does not require pyrolysis studies on pesticides that have a concentration less than 0.1 ppm at the time of harvest, and §5313 interprets this to mean that smoking 0.1 ppm of a pesticide is safe. According to the U.S. Government Accountability Office, however, the EPA does not regulate pesticides at this level simply because it assumes that they are much less toxic than the tobacco itself [17].†† Cigarette smoking is the leading preventable cause of death in the U.S., killing an estimated 480,000 people each year [18]. *Less toxic than cigarettes is not a justification for calling something safe.*

Additionally, the proposed action limits on pesticides contain internal contradictions. A number of Category 1 pesticides are not allowed because of acute toxicity, conflicting with the notion that smoking 0.1 ppm of any pesticide is safe. And if up to 70% of smoked pesticides are delivered to the lungs, then the limit for vaporized products would not need to be less than 70% of the limit on flower. Yet the proposed limits on concentrates are much less than the limits on flowers.

Revising Limits for Pesticides in Ingested Products

All of the ADI's for Category 3 pesticides, along with a comparison between our proposed limits and §5313(c), are provided in Table 6 of Appendix D: Pesticide Safety Data and Limits.

Our determination of pesticide limits on ingested cannabis products follows the same guidelines as for solvents. We use the ADIs of pesticides reported by the European Food Safety Administration (EFSA). If the EFSA does not provide the ADI for a pesticide, then we use the World Health Organization's (WHO) ADI. Maximal edible use is estimated to be 250 mg/kg/day.

No ADI could be found for prallethrin. As such, we recommend that this be moved to a Category 1 pesticide or removed entirely.

Because of the ubiquity of pesticides in food products, potential synergistic toxicity from the contribution of multiple pesticides, and the vulnerable state of many medical cannabis patients, we divide the determined action limit is divided by a factor of 40. (Note that most ADIs already have a 100-

** By comparison, the oral bioavailability of cannabinoids is 3-6% whereas the smoked bioavailability is 15-30% [15].

†† From this article: the "EPA does not assess intermediate or long-term risks [of pesticides] to smokers because of the severity of health effects linked to use of tobacco products themselves."

fold safety factor built into them.) This ensures that cannabis use will contribute to at most 2.5% of the allowable daily intake of pesticides.

Four compounds are calculated to have very high allowable limits: captan, kresoxim-methyl, fenhexamid, and piperonal butoxide. This makes some sense for piperonal butoxide — a synergist that is not a toxin in and of itself[‡‡]. The other three compounds are fungicides. 5 ppm is the highest allowable limit we recommend for these fungicides, although safe concentrations of up to 40 ppm were calculated. It may be that, as fungicides, these compounds affect pathways that are not present in animals, and hence are fairly nontoxic to humans. However, we would like to see published studies verifying the environmental and human safety of these fungicides before such high concentrations are used on cannabis.

Issues in §5313(b): ingested products

Determining the action limit for ingested products requires estimating the maximum consumption of edibles. In §5313 this parameter is estimated to be 10% of the individual's bodyweight. In other words, §5313 assumes that an average adult eats about 15 pounds of edibles per day. This is absurd. In addition, the assumption is inconsistent with §5310's solvent regulations, which assumes a maximal consumption of 10 g per day.

As well, the safety limits for ingesting pesticides in §5313 are based on the reference dose (RfD), not the ADI. The ADI of a toxin is an estimate of the maximum level of a toxin that can be ingested daily for an extended period of time. It specifically assumes that the toxin might be present for a lifetime, as would be the case for some medications. This is a more appropriate limit than the RfD, which gives a limit for a single day assuming the toxin is not regularly ingested.

Other Regulations

Some of the recommendations given in this document are dependent on changes to the manufacturing or growing regulations. These include testing grow sites for heavy metals rather than each batch of cannabis, as well as banning the use of Class 1 solvents (e.g. benzene and 1,2-dichloroethane) in the manufacturing of cannabis products.

[‡‡] Piperonal butoxide inhibits the metabolism of other pesticides, particularly pyrethrins, to allow the other pesticides to be toxic at lower concentrations. It is not clear to us whether piperonal butoxide interferes with a human's ability to metabolize pyrethrins. This exemplifies why it is essential to study synergistic toxicity between pesticides for human safety.

Appendix A: Equations relating regulatory limits to safety

Ingestion:

Variable/ parameter	Description	Units
D_{tox}	ADI of the adulterant, normalized to bodyweight	mg/kg/day
C	Maximum cannabis use per day, normalized to bodyweight	mg/kg/day
Lim	Regulatory limit of adulterant on cannabis	µg/g (ppmw)

The amount of adulterant ingested is—at most—the amount of cannabis product ingested times the regulatory limit divided by one million. Since this should not exceed the acceptable daily intake, these parameters must satisfy

$$D_{tox} \geq 10^{-6} * C * Lim$$

If D_{tox} and C are known, then the regulatory limit can be calculated as

$$Lim \leq 10^{6} * \frac{D_{tox}}{C} \qquad \text{(A1)}$$

INHALATION:

Variable/ parameter	Description	Units
x	Concentration of contaminant on cannabis. **The action limit should be an upper bound for x.**	µg/g (ppmw)
y	Concentration of contaminant in the lungs	mg/m^3
z	Concentration of contaminant in the lungs	ppmv
c_{acute}	Maximal acute cannabis use	g
V_{lung}	Minimal lung volume	L
MW	Molecular weight of contaminant	g/mol

To calculate contaminant exposure from its concentration in cannabis, maximal acute cannabis use and minimum lung volume must be estimated. The mass of adulterant in an individual's lungs is at most $x * c_{acute}$, and the concentration in the lungs is

$$y \geq \frac{x * c_{acute}}{V_{lung}}$$

or

$$z \approx \frac{y}{MW} \geq \frac{x * c_{acute}}{MW * V_{lung}}$$

The second equation is a worse approximation because it assumes the contaminant is an ideal gas. So when possible, toxicity data given in mg/m^3 should be used rather than data given in ppmv.

When the parameters in Appendix B are substituted, we get the relations

$$x \leq y \tag{A2}$$

or

$$x \leq MW * z \tag{A3}$$

APPENDIX B: PARAMETER ESTIMATES

CANNABIS INGESTION PER DAY: $C \leq 250$ MG/KG/DAY OR 10 G/DAY

It is difficult to make estimates regarding edibles. Servings containing 10 mg THC range from small chocolates (~3 g) to bags of savory snacks (~9 g per serving). There exist much more concentrated edibles, including a single brownie with 1000 mg THC. It would not make sense to normalize to cannabinoid content, since a therapeutic dose of THC or CBD can range from 1 mg to 600 mg. The estimate of 10 g/day is meant to be large, but not an absolute maximum. There are additional safety buffers incorporated in the action limits, such as a 100-fold safety factor that adjusts most ADIs. Moreover, 250 mg/kg/day is equal to 10 g/day for a 40 kg individual, which is a low weight. Heavier individuals are much less likely to exceed this consumption rate.

MAXIMAL ACUTE CANNABIS USE: $c_{acute} \leq 1$ G

This is used for inhalation. A large joint is approximately 1 g. The amount of concentrate inhaled is certainly less than the amount of flower smoked.

LUNG VOLUME: $V_{LUNG} \geq 1$ L

The total volume of two adult lungs is between 4-6 L. The total lung volume in healthy children is roughly 50 ml/kg bodyweight [19], so 1 L is a low estimate of lung volume.

APPENDIX C: SOLVENT SAFETY DATA AND LIMITS

INHALATION

When possible, proposed action limits are determined by calculating equation A2 with STELs reported in units of mg/m^3 from Cal/OSHA or NIOSH. If necessary, the action limit was equal to equation A3 using the STEL reported in ppmv. If no STEL was reported, the PEL with units of mg/m^3 was substituted into equation A2 to determine the action limit.

Table 4. Safety data and proposed action limits for solvents in inhaled products

Solvent	STEL (mg/m^3)	PEL (mg/m^3)	Our proposed action limit (ppmw)	§5310(c)'s proposed action limit
Acetone	1780	1200	1780	750
Acetonitrile	105	70	105	60
Benzene	5 [a]	1 [a]	--- [e]	1
Butane	---	1900 [c]	1900	800
Chloroform	---	9.78 [c]	9.78	2
1,2-Dichloroethane	8	4	--- [e]	2
Ethanol	---	1900 [c]	1900	1000
Ethyl acetate	---	1400 [c]	1400	400
Ethyl ether	1500	1200	1500	500
Ethylene oxide	5 [a]	2	9.83	5
Heptane	2000	1600	2000	500
Hexane	---	180 [c]	180	50
Isopropyl alcohol	1225	980	1225	500
Methanol	325	260	325	250
Methylene chloride	435	87	435	125
Naphtha	1800 [b]	400	1800	400
Pentane	1800 [b]	1800 [d]	1800	750
Petroleum ether	---	---	--- [e]	400
Propane	---	1800 [c]	1800	2100
Trichloroethylene	537	135	80 [f]	25
Toluene	560	37	560	150
Xylene (all isoforms)	655	435	655	150

a No STEL (PEL) in mg/m^3. STEL (PEL) in ppmv used instead. Limit calculated with equation A3.
b No STEL available from Cal/OSHA. STEL from NIOSH used. [7]
c No STEL available from Cal/OSHA or NIOSH. PEL used instead.
d Although Cal/OSHA reports the PEL of pentane as 1800 mg/m^3, NIOSH reports it to be 350 mg/m^3 [5,8]. OSHA reports it as 2950 mg/m^3.
e We propose that these chemicals are banned for use in cannabis manufacturing.
f The calculated ingestion limit was lower than the inhalation limit, so the ingestion limit is used. [10]

Ingestion

Proposed action limits are determined by calculating equation A1 with the ADIs given by USP's, assuming a consumption of 10 g/day.

Table 5. Proposed action limits for solvents in ingested products

Solvent	Our proposed action limit (ppmw)	§5310(c)'s proposed action limit
Acetone [a]	5000	5000
Acetonitrile	410	410
Benzene	--- [d]	2
Butane [b]	5000	5000
Chloroform	60	60
1,2-Dichloroethane	--- [d]	5
Ethanol [a]	--- [e]	5000
Ethyl acetate [a]	5000	5000
Ethyl ether [a]	5000	5000
Ethylene oxide	10	50
Heptane [a]	5000	5000
Hexane	290	290
Isopropyl alcohol [a]	5000	5000
Methanol	3000	3000
Methylene chloride	600	600
Naphtha	4500	400
Pentane [a]	5000	5000
Petroleum ether	--- [d]	400
Propane [c]	5000	5000
Trichloroethylene	80	80
Toluene	890	890
Xylene (all isoforms)	2170	2170

a All class 3 solvents are considered safe for ingestion of up to 50 mg/day.

b Based on OSHA's determination of butane to be generally recognized as safe. [13]

c According to the FDA, propane is GRAS. [6]

d We propose that these chemicals are banned for use in cannabis manufacturing.

e Given the established safety of a cannabis product that contains 50% ethanol by volume, we propose that there be no limit on ethanol concentration in edibles, although these products must be clearly labeled [12].

APPENDIX D: PESTICIDE SAFETY DATA AND LIMITS

CATEGORIZATION OF PESTICIDES

The pesticides classified as Category 3 were taken from §5313(b)'s list of allowable pesticides (except for prallethrin, which we listed as a Category 1 pesticide because of a lack of safety data). We spoke with Sonoma Lab Works, a cannabis testing lab, to determine the commonly used banned pesticides that should be classified as Category 2. This may not be representative of all of CA. The rest of the pesticides listed in §5313(b) were set as Category 1 pesticides. Glyphosate was added as a Category 1 pesticide.

(Continued on next page.)

INGESTION

The ADIs are based on reports by the European Food Safety Administration when possible, or the World Health Organization otherwise. The proposed action limit is then calculated using equation A1. Only Category 3 pesticides are listed below (pesticides which are not prohibited from use on cannabis).

Table 6. Safety data, references, and proposed action limits for pesticides in ingested products

Click pesticide name to view reference for ADI.

Pesticide	ADI (mg/kg)	Our proposed action limit (ppmw)	§5313(b)'s proposed action limit
Acequinocyl	0.023	2.3	0.27
Bifenazate	0.01	1	1
Captan	0.1	5 [a]	1
Clofentezine	0.02	2	1.3
Cypermethrin	0.0016	0.16	1
Etoxazole	0.05	5	0.46
Fenhexamid	0.2	5 [a]	1.7
Fenpyroximate	0.01	1	0.5
Flonicamid	0.025	2.5	0.4
Hexythiazox	0.03	3	0.25
Kresoxim-methyl	0.4	5 [a]	3.6
Oxamyl	0.001	0.1	0.026
Pentachloronitrobenzene (Quintozene)	0.01	1	0.03
Permethrin	0.05	5	2.5
Phosmet	0.01	1	0.12
Piperonyl butoxide	0.2	20 [b]	63
Pyrethrins	0.04	4	0.7
Pyridaben	0.01	1	4.4
Spinetoram	0.025	2.5	0.5
Spinosad	0.02	2	0.29
Spiromesifen	0.03	3	20
Spirotetramat	0.05	5	10
Trifloxystrobin	0.04	4	25

a These calculated action limit was higher than 5 ppm for these fungicides. The maximum action limit for any pesticides was set at 5 ppm.

b Piperonal butoxide's action limit is higher than 5 ppm because it is not a pesticide. It is a synergist that inhibits the degradation of other pesticides by insects, particularly pyrethrins.

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