

April 29, 2019

Julian Leichthy
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010

Re: Comments Regarding the Reproductive Toxicity (Developmental Toxicity Endpoint) of Cannabis and Cannabis-Related Chemicals

Dear Mr. Leichthy:

Keller and Heckman LLP is pleased to submit comments to California's Office of Environmental Health Hazard Assessment (OEHHA) in response to its "Request for Relevant Information on the Reproductive Toxicity (Developmental Toxicity Endpoint) of Cannabis and Cannabis-Related Chemicals," issued on March 15, 2019. The request for comments is intended to inform the Developmental and Reproductive Toxicant Identification Committee (DARTIC) of OEHHA's Science Advisory Board, which serves as the state's qualified experts for purposes of listing new chemicals under Proposition 65 (*i.e.*, The Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code section 25249.5 *et seq.*).

Keller and Heckman LLP represents interested parties in cannabis and cannabis-related industries. In the March 15, 2019 request for comments, OEHHA requested relevant information on the reproductive (*i.e.*, developmental) toxicity of cannabis (marijuana), marijuana (cannabis) smoke, cannabis extracts, and Δ -9-tetrahydrocannabinol (THC). Our comments below specifically address the proposed listing of "cannabis extracts." As discussed below, we do not believe there are adequate data to support that "cannabis extracts" are "known to the state to cause" reproductive toxicity when the composition of "cannabis extracts" can vary dramatically based on the extraction method, solvent, and cannabis strain. Thus, we respectfully submit that OEHHA should consider listing only the specific extracts if they are "known to the state to cause" reproductive toxicity.

I. "Cannabis Extracts" Is Too Broad a Term and Refers to Potentially Myriad Different Mixtures

In the absence of a definition of the term "Cannabis Extracts," the term would be interpreted to refer to any substance or substances extracted from the cannabis (marijuana)

plant. Depending on the extraction method, solvent, and cannabis strain, the composition of the extract will vary dramatically. It is apparent from the World Health Organization's Expert Committee on Drug Dependence Critical Review of Cannabis and Cannabis resin that there are a number of different techniques used to extract components from cannabis.¹ The chemical composition of an "extract" depends on many factors, including extraction method and plant matrix.² For example, the most common compounds extracted from cannabis are Δ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD). These substances are non-polar and expected to be readily extracted by non-polar solvents (*e.g.*, oil-based solvents); however, these substances would not be readily extracted in a polar solvent (*e.g.*, water). Different extracts would be produced by using different non-polar or polar solvents in that different solvents will produce mixtures with differing compounds at different ratios.

In fact, differences in cannabis extract composition are observed even within the same extraction method when extraction parameters vary. For example, Rovetto and Aieta (2017) and Da Porto (2014) observed differences in cannabis extracts using supercritical CO₂.³ Similarly, Hazekamp *et al.* (2004) describe differences in the composition of extracts produced using centrifugal partition chromatography (CPC).⁴ Differences in composition can also be found in products already on the market. Pavlovic *et al.* (2018) examined the cannabinoid content of off-the-shelf hemp oils available in Europe and found cannabinoid content varied considerably from product to product.⁵ This variation was not restricted to the primary component (CBD), and was

¹ WHO (2018), World Health Organization Expert Committee on Drug Dependence, Critical Review: Cannabis and Cannabis Resin, available at, <https://www.who.int/medicines/access/controlled-substances/Extracts-and-tinctures.pdf?ua=1>.

² Azmir J., *et al.* (2013), Techniques for extraction of bioactive compounds from plant materials: A review, 117 *Journal of Food Engineering*. 117: 426-36.

³ Rovetto L. and Aieta N. (2017), Supercritical carbon dioxide extraction of cannabinoids from *Cannabis sativa L.* plant material. *The Journal of Supercritical Fluids*. 129:16-27; Da Porto C., *et al.* (2014) Separation of aroma compounds from industrial hemp inflorescences (*Cannabis sativa L.*) by supercritical CO₂ extraction and on-line fractionation. *Industrial Crops and Products*. 58: 99-103.

⁴ Hazekamp A., *et al.* (2004), Preparative Isolation of Cannabinoids from *Cannabis sativa* by centrifugal partition chromatography. *Journal of Liquid Chromatography & Related Technologies*. 27(15): 2421-39.

⁵ Pavlovic R., *et al.* (2018), Quality Traits of "Cannabidiol Oils": Cannabinoids Content, Terpene Fingerprint and Oxidation Stability of European Commercially Available Preparations. *Molecules*. 23 (5): 1230.

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also reflected in the relative and absolute content of other cannabinoids. Similar variations have been reported for commercial products available in the US. Lot analyses supplied to the U.S. Food and Drug Administration (FDA) in support of GRAS (*i.e.*, “Generally Recognized As Safe”) Notice (GRN) 778 indicate that even hemp products, which have been cleared for use in human food, can vary in the amounts of various cannabinoids by as much as 10-fold.⁶

Cannabis also includes a number of different strains with different compositions. Traditionally, cannabis varieties have been sorted into “chemotypes” based on the relative ratio of THC and CBD contained in the plant, with Type I containing more THC, Type II containing equal amounts of the compounds, and Type III containing more CBD.⁷ However, as more chemical compounds from cannabis besides THC and CBD gain commercial relevance, additional research on the mix of chemical compounds found in various strains has indicated that the number of strains and relative chemical compositions vary considerably—more than the traditional approach of classification based on THC:CBD content would indicate.⁸

Because the composition of a cannabis extract will depend on many factors, including the specific variety or strain of plant and extraction parameters, it is difficult to imagine all “cannabis extracts” can be demonstrated to satisfy the threshold criterion for listing by the state’s qualified experts under Section 25249.8(b) of Proposition 65 that the extracts are “known to the state to cause” reproductive toxicity when the composition of a cannabis extract is so dependent on the method of extraction, the strain of cannabis, and the solvent. Further, we stress there are no other examples of listed chemicals on Proposition 65 that have the potential to refer to widely variable mixtures of substances.

⁶ Fresh Hemp Foods Ltd. (2018), GRN 778 Submission to FDA (“The Safety and Generally Recognized as Safe (GRAS) Status of the Proposed Use of Hemp Oil in Human Food”), available at <https://wayback.archive-it.org/7993/20190213183735/https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/UCM625546.pdf>.

⁷ Hillig K., and Mahlberg P. (2004) A chemotaxonomic analysis of cannabinoid variation in Cannabis (*Cannabaceae*). *American Journal of Botany*. 91: 966–975.

⁸ Mudge E., *et al.* (2018) Chemometric analysis of cannabinoids: chemotaxonomy and domestication syndrome. *Scientific Reports*. 8: 13090; Mechtler K., *et al.* (2004) Variations of Δ9-THC content in single plants of hemp varieties. *Industrial Crops and Products*. 19 (1): 19-24.

II. It Is Not Appropriate to List All “Cannabis Extracts” As Being “Known to the State to Cause” Reproductive Toxicity OEHHA without Evidence on Each Specific Cannabis Extract

As discussed above, the composition of cannabis extracts will vary dramatically depending on the method of extraction, the solvent, and the cannabis strain. It is almost certainly the case that, even if there are adequate data demonstrating specific individual chemicals in cannabis extracts are “known to the state to cause reproductive toxicity,” there will be other extracts that are not “known to the state to cause” reproductive toxicity. Section 25249.8 of the statute requires DARTIC to determine that a chemical be “clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity” for the chemical to be listed under Proposition 65. Based on our research, it is clear “cannabis extracts” do not refer to a single commodity or mixture and—with the exception of the most abundant cannabinoid compounds (THC and CBD)—there are limited safety data on most “cannabis extracts.”² What data are available in the public literature that assess the developmental or reproductive toxicity of cannabis focuses almost entirely on THC and CBD.¹⁰ Thus, we respectfully submit that the categorical listing of “cannabis extracts” would be inappropriate in that it would capture thousands of cannabis extracts that have no evidence of any reproductive toxicity concern. Rather, we recommend the state focus on evaluating whether specific chemicals or specific extracts present reproductive toxicity concern and therefore require listing.

² Sharma P., *et al* (2012) Chemistry, Metabolism, and Toxicology of Cannabis: Clinical Implications. *Iran J Psychiatry*. 7(4) 149-156; Iffland, K. and Grotenhermen, F. (2017) An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. *Cannabis and Cannabinoid Research*. 2 (1): 139-154.

¹⁰ See NIH U.S. National Library of Medicine, Toxicology Data network (TOXNET), Developmental and Reproductive Toxicity (DART) Database, available at <https://toxnet.nlm.nih.gov/newtoxnet/dart.htm>.

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We appreciate the opportunity to submit these comments and welcome any follow-up questions that OEHHA may have.

Cordially yours,



Evangelia C. Pelonis