

Clinicians' Institute for Cannabis Medicine

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To Lawmakers:

We are physicians who are concerned that HB13-1114 will label as impaired large numbers of medical marijuana patients who are not impaired, yet who may test continuously above 5 ng/mL THC in blood because of long term, high dose cannabis therapy.

Models relating impairment to blood levels were developed with studies of occasional users (A). Yet in long term and high dose users, THC blood level and impairment do not correlate well at all (B). These results may be surprising, but they can be understood from the clear science around three aspects of THC and cannabinoids:

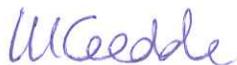
1. Only a small portion of total THC in blood is active, because most of it is bound to plasma proteins – and the more THC in the blood, the less is active (C).
2. THC psychoactivity is blocked by cannabidiol (CBD), which has significant therapeutic effects and is not psychoactive, and allows higher THC levels to be used without more psychoactivity (D).
3. Tolerance to effects of THC readily develops, and psychoactive tolerance occurs more quickly than does tolerance to other effects like pain relief (E).

These factors reduce the psychoactive effect of a given THC blood level in long term, high dose users. This is why blood THC levels in long term, high dose users correlate very poorly with psychoactivity and impairment. A per se limit would be punitive and unfair to patients who intentionally use cannabis in ways that minimize impairment and increase therapeutic benefit, but may cause high total THC blood levels.

This limit may force patients who seek to comply with the law to take dangerous and expensive pharmaceutical medications that do not have nanogram per se limits and are not routinely tested for by the police, but that may have equal or greater potential for impairment as cannabis.

We urge you either to not pass this bill, or to add an exemption for registered medical marijuana patients.

With best regards,



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Supporting Information

A. Blood Impairment Levels Were Developed in Occasional Users

Chem Biodivers. 2007 Aug;4(8):1770-804. Human cannabinoid pharmacokinetics. Huestis MA. PMID: 17712819.

B. Blood THC Does Not Predict Impairment in Frequent Users

J Anal Toxicol. 2012 Jul;36(6):405-12. Psychomotor performance, subjective and physiological effects and whole blood Δ 9-tetrahydrocannabinol concentrations in heavy, chronic cannabis smokers following acute smoked cannabis. Schwoppe DM, Bosker WM, Ramaekers JG, Gorelick DA, Huestis MA. PMID: 22589524.

J Psychopharmacol. 2009 May;23(3):266-77. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR. PMID: 18719045.

J Anal Toxicol. 2008 Sep;32(7):470-7. Comparison of cannabinoid pharmacokinetic properties in occasional and heavy users smoking a marijuana or placebo joint. Toennes SW, Ramaekers JG, Theunissen EL, Moeller MR, Kauert GF. PMID: 18713514. "Cannabinoid pharmacokinetics in occasional users is well studied, but the interpretation of data from heavy users is difficult.... The results obtained with occasional users were in contrast to those of the heavy users.... Of the 12 heavy users, 10 exhibited up to 12.3 microg/L [ng/mL] Delta(9)-tetrahydrocannabinol (THC) prior to smoking."

Traffic Inj Prev. 2006 Jun;7(2):111-6. Relationship between THC concentration in blood and impairment in apprehended drivers. Khiabani HZ, Bramness JG, Bjørneboe A, Mørland J. PMID: 16854704. Suspected drugged drivers in Norway who were judged not to be impaired had THC blood levels as high as 24 ng/mL THC.

C. Higher Levels of THC Are Made Inactive in the Blood by Protein Binding

IUBMB Life. 2011 Jun;63(6):446-51. Binding of δ 9-tetrahydrocannabinol and diazepam to human serum albumin. Fanali G, Cao Y, Ascenzi P, Trezza V, Rubino T, Parolaro D, Fasano M. PMID: 21557446. "THC binds to two different binding sites of human serum albumin... THC binding to the high-affinity site accounts for the low free fraction of the drug in plasma."

Marinol (Dronabinol) Package Insert – Abbott Laboratories: "The plasma protein binding of dronabinol [THC] and its metabolites is approximately 97%."

D. Psychoactive Effects of THC Are Blocked by Other Cannabinoids

Curr Pharm Des. 2012;18(32):4897-905. Potential protective effects of cannabidiol on neuroanatomical alterations in cannabis users and psychosis: a critical review. Hermann D, Schneider M. PMID: 22716143.

Neuropsychopharmacology. 2010 Feb;35(3):764-74. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Bhattacharyya S, et al. PMID: 19924114.

Br J Pharmacol. 2008 Jan;153(2):199-215. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Pertwee RG. PMID: 17828291.

Br J Pharmacol. 2007 Mar;150(5):613-23. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. PMID: 17245363.

Med Hypotheses. 2006;66(2):234-46. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Russo E, Guy GW. PMID: 16209908.

Neuropharmacology. 2004 Dec;47(8):1170-9. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G. PMID: 15567426.

Eur J Pharmacol. 2002 Dec 5;456(1-3):99-106. (-)-Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens. Pertwee RG, Ross RA, Craib SJ, Thomas A. PMID: 12450575.

Psychopharmacology (Berl). 1982;76(3):245-50. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. PMID: 6285406.

Psychopharmacologia. 1974;38(4):329-38. Modification of delta9-THC-actions by cannabinal and cannabidiol in the rat. Fernandes M, Schabarek A, Coper H, Hill R. PMID: 4473791.

Different THC:CBD dosing ratios have different therapeutic effects. GW Pharmaceuticals has patented four THC-CBD combinations for four categories of medical conditions. US Patent 6946150 B2. "Pharmaceutical Formulation". GW Pharma Ltd.

E. Frequent Users Develop Tolerance to Psychoactive Effects

Neuropsychopharmacology 2008;33:2505-2016. Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. D'Souza et al. "These data suggest that frequent users of cannabis are either inherently blunted in their response to, and/or develop tolerance to the psychotomimetic, perceptual altering, amnestic, endocrine, and other effects of cannabinoids."

AAPS J. 2006 Mar 10;8(1):E112-7. Activation of G-proteins in brain by endogenous and exogenous cannabinoids. Childers SR. PMID: 16584117. "Chronic treatment in vivo with cannabinoids produces significant tolerance to the physiological and behavioral effects of these drugs."

Handb Exp Pharmacol. 2005;(168):691-717. Cannabinoid tolerance and dependence. Lichtman AH, Martin BR. PMID: 16596793.

Eur J Pharmacol. 2005 Mar 7;510(1-2):59-68. Task specificity of cross-tolerance between Delta9-tetrahydrocannabinol and anandamide analogs in mice. Wiley JL, Smith FL, Razdan RK, Dewey WL. PMID: 15740725.

Behav Pharmacol. 2004 Feb;15(1):1-12. Behavioral effects of cannabinoids show differential sensitivity to cannabinoid receptor blockade and tolerance development. De Vry J, Jentzsch KR, Kuhl E, Eckel G. PMID: 15075621.

Crit Rev Neurobiol. 2003;15(2):91-119. Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. Sim-Selley LJ. PMID: 14977366.

J Pharmacol Exp Ther. 2002 Oct;303(1):36-44. Effect of chronic administration of R-(+)-[2,3-Dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate (WIN55,212-2) or delta(9)-tetrahydrocannabinol on cannabinoid receptor adaptation in mice. Sim-Selley LJ, Martin BR. PMID: 12235230.