November 22, 2016

Christine Leonard, Director
Office of Legislative and Public Affairs
United States Sentencing Commission
(202) 502-4500
pubaffairs@ussc.gov

Dear Ms Leonard,

With regard to the Sentencing Commission review of the Guidelines that pertain to Synthetic Cannabinoids, I respectively submit the attached documents documents which support consideration of reducing the current 1:167 ratio.

Attached are three documents that support our position, including the Sentencing Order USA vs Hossain, whereas 11th District Judge Middlebrooks sentenced Hossain at a 1:7 ratio as opposed to the Sentencing Guidelines ratio of 1:167, stating in part, "I find it troubling that there does not seem to be any reason behind the 1:167 ratio.Although I asked each of the experts at the hearing, no one could provide me with a reason for this ratio, which has major implications in determining the base level offense. After my own research and a phone call to the Sentencing Commission, I still could find no basis for this ratio. It
appears to have been included in the first set of Guidelines in 1987, with no published explanation."

Judge Middlebrooks goes on to say, "We know from Government studies that the average THC content in marijuana today is over 14 percent. So the ratio should be one to seven, not one to 167... This sentence range is more reasonable than the sentence that the Government suggests I impose, based off the 1:167 ratio".

Ms Leonard , also attached are the University of Mississippi Government studies that Judge Middlebrooks references, as well as, the declaration of Dr Nicholas Cozzi, University of Wisconsin School of Medicine and Public Health.

Ms Leonard, no one knows where the 167:1 ratio comes from. Research and data support the more reasonable 1:7 ratio. Sentencing reform can rest on many levels. Not just Congress. The Sentencing Commission has undertaken this review and we strongly urge you to consider these facts.

Thank you for your's and the Committee's consideration. Please keep us informed as to the status of meetings and updates as they pertain toward these issues.

Sincerely,
Jim Barrow

December 1, 2016

Christine Leonard, Director
Office of Legislative and Public Affairs
United States Sentencing Commission
(202) 502-4500
pubaffairs@ussc.gov

Dear Ms Leonard,

As a supplement to my letter of November 22, 2016, a copy of which is attached, I would like to make an additional statement.

The Commission review of Number 9 of the Priorities mentions in part the synthetic cannabinoid compounds JWH-018 and AM-2201.

While my original letter proposes new guidelines for these substances I think I should be clear that what really needs to be reviewed is the guideline for THC. The Guideline for THC is where the 167:1 multiplier originates. The courts have determined that THC is the most closely related substance to JWH-018 and AM-2201. That is the reason why these substances are likewise given the guideline of 167:1.

Ms Leonard, since the courts have determined this relationship, we are not challenging the relationship of these substances to THC. But we do question the 167:1 multiplier assigned to THC. The University of Mississippi Government study concluded that the average percentage of THC in marijuana is greater than 14%,which supports the 1:7 ratio Judge Middlebrooks used in the Hossain sentencing, as well as the declaration of Dr Nicholas Cozzi, University of Wisconsin School of Medicine and Public Health.

I have attached my original letter plus these supporting documents for review.

Thank you again for your's and the Committee's consideration and please keep us informed as to the status of meetings and updates as they pertain toward these issues.

Sincerely,

Jim Barrow

February 2, 2017

Christine Leonard, Director
Office of Legislative and Public Affairs
United States Sentencing Commission
(202) 502-4500
pubaffairs@ussc.gov

Dear Ms Leonard,

I trust that your new year is off to a great start.

I appreciate you accepting the letters and supplements that I've submitted to you and the committee in consideration of a reassessment of the synthetic cannabinoid compounds sentencing guidelines.

I see that the Commission has committed to a two-year study. But what exactly are they studying? The effects of the compounds like AM-2201? Several experts on both sides have testified to this already. Are they studying the fairness of disparity in sentences? This information is readily available. Notwithstanding the numerous cases around the country where the sentencing guidelines have ranged from 1:1, 1:7 and upwards to the 1:167, take for instance USA vs Reece. Here Reece, the number one defendant, was sentenced to 6 months home confinement because he was able to get his sentencing moved to his home state of Florida. The sentencing judge completely through out the 1:167. Meanwhile, his co-defendants in Louisiana were sentenced at 1:167 from 4-10 years incarceration.

While I appreciate that the commission has committed to a two-year study I urge the Commission to look at this from another point that would save the commission, the taxpayers and the defendants involved considerable time and resources.

With respect to Synthetic Cannabinoids, the Commission and the Courts were asked to determine the “most closely related substance”. In doing so, the Commission found that THC was the most closely related. Some Courts have agreed while many others have not because of the very high 1:167 multiplier. Chemically speaking THC may be the most closely related drug in the Guidelines. The problem with that is the THC multiplier that ends up being assigned these other compounds that many judges do not agree.

Attached are three documents that support our position, including the Sentencing Order USA vs Hossain, whereas 11th District Judge Middlebrooks sentenced Hossain at a 1:7 ratio as opposed to the Sentencing Guidelines ratio of 1:167, stating in part, "I find it troubling that there does not seem to be any reason behind the 1:167 ratio.Although I asked each of the experts at the hearing, no one could provide me with a reason for this ratio, which has major implications in determining the base level offense. After my own research and a phone call to the Sentencing

Commission, I still could find no basis for this ratio. It appears to have been included in the first set of Guidelines in 1987, with no published explanation."

Judge Middlebrooks goes on to say, "We know from Government studies that the average THC content in marijuana today is over 14 percent. So the ratio should be one to seven, not one to 167... This sentence range is more reasonable than the sentence that the Government suggests I impose, based off the 1:167 ratio".

Ms Leonard , also attached are the University of Mississippi Government studies, funded by the National Institute on Drug Abuse, that Judge Middlebrooks references, as well as, the declaration of Dr Nicholas Cozzi, University of Wisconsin School of Medicine and Public Health.

Maybe the immediate issue before the Commission is not further studies on synthetic cannabinoids but to reassess the THC guideline. There is no further research or government or taxpayers resources required for this. The study has been done. The attached University of Mississippi study was funded by our government.

The current sentencing guidelines for the compounds marijuana and THC state:

SCHEDULE I MARIHUANA CONVERTED DRUG WEIGHT
1 gm of Marihuana/Cannabis, granulated, powdered, etc. = 1 gm of marihuana
1 gm of Tetrahydrocannabinol, Organic = 167 gm of marihuana
1 gm of Tetrahydrocannabinol, Synthetic = 167 gm of marihuana

If we know from the University of Mississippi government funded study that the current average potency in marijuana is 14% THC, how can the 1:167 ratio for THC stand?

Ms Leonard, no one knows where the 1:167 ratio comes from. Research and data support the more reasonable 1:7 ratio. Sentencing reform can rest on many levels. Not just Congress. The Sentencing Commission has undertaken this review and we strongly urge you to consider these facts.

Thank you for your's and the Committee's consideration. Please keep us informed as to the status of meetings and updates as they pertain toward these issues.

Sincerely,

Jim Barrow

# U.S. v. HOSSAIN

Case No. 15-cr-14034-MIDDLEBROOKS.



*UNITED STATES, Plaintiff, v. SAIFUL HOSSAIN, AHMED YEHIA KHALIFA, and AHMED MAHER ELHELW, Defendant.*

United States District Court, S.D. Florida.

January 5, 2016.



***Attorney(s) appearing for the Case***

*Saiful Hossain, Defendant, represented by Richard G. Lubin, Richard G. Lubin, PA & Fritz Joseph Scheller, Fritz Scheller, P.L..*

*Ahmed Yehia Khalifa, Defendant, represented by Mark Jon O'Brien.*

*Ahmed Maher Elhelw, Defendant, represented by Marc Shiner, Perlet & Shiner PA.*

*USA, Plaintiff, represented by Carmen M. Lineberger, U.S. Attorney's Office & Antonia J. Barnes, United States Attorney's Office.*

## SENTENCING ORDER

**DONALD M. MIDDLEBROOKS**, *District Judge*.

Defendant Saiful Hossain pleaded guilty to Counts I and II of the Superseding Indictment. Count I charges Hossain with conspiracy to import a controlled substance— XLR-11—in violation of 21 U.S.C. §§ 952(a) and 963. Count II charges him with conspiracy to manufacture, possess with intent to manufacture and

distribute a controlled substance—XLR-11—in violation of 21 U.S.C. §§ 841(a)(1) and 846. (DE 84).

XLR-11, a temporarily controlled substance, is not referenced in the Drug Quantity Table or Drug Equivalency Table of Section 2D 1.1 of the United States Sentencing Guidelines ("Guidelines"). 18 U.S.C. § 2D1.1. I held a hearing on December 11, 2015 to hear evidence on how XLR-11 should be considered at sentencing. On January 5, 2016, I heard argument on the role of Hossain in the instant offense, as well as § 3553 factors.

## I. Background

XLR-11 is a "synthetic cannabinoid." [1] Synthetic cannabinoids act on two receptors in the human body, CB1 and CB2, to cause a "high" similar to what users experience while consuming marijuana. XLR-11, like other synthetic cannabinoids, typically comes to the United States from China as a powder, which is then applied to plant materials to be smoked, or liquidated to be used in vaporizers. (DE 229, Tr. at 65). Synthetic cannabinoids laced on plant materials are often marked as "herbal incense" products and can be purchased online or at gas stations.

Reports of XLR-11 use in the United States began in the first half of 2012. Because XLR-11 appeared only three years ago in the United States, knowledge about XLR-11 is limited. (DE 217-4, *Acute Kidney Injury Associated with Synthetic Cannabinoid Use).* Information about the effects of XLR-11 is further limited because in the synthetic drug market it is common for the drugs to be replaced by new, unregulated chemicals once one synthetic has been regulated. By one account, products are available for only about twelve to twenty four months before they are replaced by the next, unregulated wave. (DE 217-8, *Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs).*

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**PAPER**

**CRIMINALISTICS**

*Zlatko Mehmedic,*[1] *M.Sc.Pharm.; Suman Chandra,*[1] *Ph.D.; Desmond Slade,*[1] *Ph.D.; Heather Denham,*[1] *B.A.; Susan Foster,*[1] *B.A.; Amit S. Patel,*[2,3] *Ph.D.; Samir A. Ross,*[1,4] *Ph.D.; Ikhlas A. Khan,*[1,4] *Ph.D.; and Mahmoud A. ElSohly,*[1,5] *Ph.D.*

# Potency Trends of $\Delta^9$-THC and Other Cannabinoids in Confiscated Cannabis Preparations from 1993 to 2008*

**ABSTRACT:** The University of Mississippi has a contract with the National Institute on Drug Abuse (NIDA) to carry out a variety of research activities dealing with cannabis, including the Potency Monitoring (PM) program, which provides analytical potency data on cannabis preparations confiscated in the United States. This report provides data on 46,211 samples seized and analyzed by gas chromatography-flame ionization detection (GC-FID) during 1993–2008. The data showed an upward trend in the mean $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) content of all confiscated cannabis preparations, which increased from 3.4% in 1993 to 8.8% in 2008. Hashish potencies did not increase consistently during this period; however, the mean yearly potency varied from 2.5–9.2% (1993–2003) to 12.0–29.3% (2004–2008). Hash oil potencies also varied considerably during this period (16.8 ± 16.3%). The increase in cannabis preparation potency is mainly due to the increase in the potency of nondomestic versus domestic samples.

**KEYWORDS:** cannabichromene (CBC), cannabidiol (CBD), cannabigerol (CBG), cannabinoids, cannabinol (CBN), cannabis, criminalistics, forensic science, gas chromatography-flame ionization detection (GC-FID), marijuana, potency, tetrahydrocannabivarin (THCV), $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC)

Marijuana, the crude drug derived from *Cannabis sativa* L. pistillate inflorescence, is the most widely cultivated and consumed illicit drug in the world despite being under international control for eight decades (1,2). The reason for this is mainly attributed to two factors; namely, relaxation of cannabis law enforcement relative to other illicit drugs and the enormous extent of cannabis production and consumption. Furthermore, cannabis is cultivated both indoors and outdoors, often on a small scale, facilitating inconspicuous trading. Hashish (hash) and hash oil are two preparations designed to minimize the volume of the drug, thereby minimizing confiscation.

The $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) potency (concentration or content) of cannabis depends on soil and climate conditions, variety (phenotype), and cultivation techniques, with different parts of the plant having varying concentrations of the drug (3–6). The total number of identified cannabis constituents has increased from 489 in 2005 (7) to 537 in 2009, while the number of cannabinoids has increased from 70 to 109 (8–13). The main psychoactive ingredient in cannabis is $\Delta^9$-THC (14,15); however, other cannabinoids have also demonstrated pharmacological activities, e.g., the nonpsychotropic cannabinoid cannabidiol (CBD) displays antipsychotic, antihyperalgesic, anticonvulsant, neuroprotective, and antiemetic properties (16–18).

The complex political, medical, cultural, and socioeconomic issues associated with cannabis necessitates not only public and governmental scrutiny, but especially scientific inquiry (1,2,19–24). The National Institute on Drug Abuse (NIDA) Potency Monitoring (PM) program at the National Center for Natural Products Research, University of Mississippi, provides analytical potency data on cannabis preparations seized in the United States, including both domestic and nondomestic material (25–28). A survey of the literature reporting similar programs in other countries revealed a number of comprehensive studies, e.g., England (2004–2005) (29), Brazil (2006–2007) (30), Netherlands (1999–2007) (31–34), Italy (1997–2004) (35), New Zealand (1976–1996) (36), and Australia (37), as well as a number of general reviews pertaining to cannabis potency trends (1,2,21,22,32,38,39).

This report covers 46,211 cannabis preparations confiscated and analyzed by gas chromatography-flame ionization detection (GC-FID) in the United States during 1993–2008, following on previous reports covering 1972–1997 (36,297 samples) (25–28). The total number of samples received during this period (1993–2008) was 47,583 as of 30 March 2009. The number of samples analyzed was 46,211, with 1,372 samples not analyzed for a variety of reasons, including insufficient material, wet material, and material containing only seeds and stems. Statistical analysis on the mean yearly $\Delta^9$-THC concentration is included to establish the potency trend over time. Data on hashish, hash oil, and the potencies of

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*This project was supported by the National Institute on Drug Abuse (contract number N01DA-5-7746).

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cannabichromene (CBC), cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV) are also presented.

## Materials and Methods

### *Sample Acquisition*

All samples analyzed in this investigation were confiscated during 1993 through 2008 by United States Federal and State law enforcement agencies.

### *Sample Identification*

Sample classification is based on physical characteristics according to the following guidelines:

*Cannabis Samples*—All samples were received as raw plant material. These samples were further categorized as follows:

- *Marijuana* (known as herbal cannabis in Europe): usually found in four forms: (i) loose material - loose cannabis plant material with leaves, stems, and seeds; (ii) leaves - cannabis plant material consisting primarily of leaves; (iii) kilo bricks - compressed cannabis with leaves, stems, and seeds (typical Mexican packaging); and (iv) buds - flowering tops of female plants with seeds.
- *Sinsemilla*: flowering tops of unfertilized female plants with no seeds (subdivided as for marijuana with most samples being classified as buds).
- *Thai sticks*: leafy material tied around a small stem (typical Thailand packaging).
- *Ditchweed*: fiber type wild cannabis found in the Midwestern region of the United States (subdivided as for marijuana).

*Hashish Samples*—Hashish (known as cannabis resin in Europe) is composed of the resinous parts of the flowering tops of cannabis, mixed with some plant particles and shaped into a variety of forms, e.g., balls, sticks, or slabs. It is generally very hard with a dark green or brownish color.

*Hash Oil Samples*—Hash oil is a liquid or semi-solid concentrated extract of cannabis plant material. Depending on the process used to prepare hash oil, it is usually dark green, amber, or brownish.

### *Sample Storage*

All samples are stored in a vault at controlled room temperature (17 ± 4°C).

### *Domestically Cultivated Cannabis*

Cannabis preparations that have been verified as being produced from plants grown in the United States are classified as domestic samples, whereas all other samples are classified as nondomestic.

### *Sample Preparation*

*Cannabis*—The samples were manicured in a 14 mesh metal sieve to remove seeds and stems. Duplicate samples (2 × 0.1 g) were extracted with internal standard solution (ISTD) [3 mL, 4–androstene-3,17-dione (100 mg) (Sigma Aldrich, St. Louis, MO) in chloroform/methanol (100 mL, 1:9, v/v), 1 mg/mL] at room temperature for 1 h. The extracts were transferred to GC vials via filtration through sterile cotton plugs, followed by capping of the vials (25).

*Hashish*—Samples were powdered using a mortar and pestle or an electric blender. Duplicate samples (2 × 0.1 g) were extracted following the procedure outlined for cannabis samples (*vide supra*).

*Hash Oil*—Duplicate samples (2 × 0.1 g) were extracted with ISTD [4 mL, 4-androstene-3,17-dione (50 mg) in absolute ethanol (50 mL), 1 mg/mL] as follows: maceration at room temperature for 2–4 h, sonication for 5 min, addition of absolute ethanol (20 mL), and sonication for 5 min. The extracts were transferred to GC vials as described earlier.

### *Chromatographic Analysis*

GC analyses were performed using Varian CP-3380 gas chromatographs, equipped with Varian CP-8400 automatic liquid samplers, capillary injectors, dual flame ionization detectors, and DB-1MS columns (15 m × 0.25 mm × 0.25 μm) (J&W Scientific, Folsom, CA). Data were recorded using a Dell Optiplex GX1 computer and Varian Star workstation software (version 6.1). Helium was used as carrier and detector makeup gas with an upstream indicating moisture trap and a downstream indicating oxygen trap. Hydrogen and compressed air were used as the combustion gases. The following instrument parameters were employed: air, 30 psi (300 mL/min); hydrogen, 30 psi (30 mL/min); column head pressure, 14 psi (1.0 mL/min); split flow rate, 100 mL/min; split ratio, 50:1; septum purge flow rate: 5 mL/min; makeup gas pressure, 20 psi (30 mL/min); injector temperature, 240°C; detector temperature, 270°C; oven program, 170°C (hold 1 min) to 250°C at 10°C/min (hold 3 min); run time, 12 min; injection volume, 1 μL. The instruments are daily maintained and calibrated to ensure a $\Delta^9$-THC/internal standard response factor ratio of one.

### *Calculation of Concentrations*

The concentration of a specific cannabinoid is calculated as follows:

$$cannabinoid\% = \frac{GC[area](cannabinoid)}{GC[area](ISTD)} \times \frac{amount(ISTD)}{amount(sample)} \times 100$$

### *Statistical Analysis*

The mean and standard deviation (SD) of the sample concentrations were calculated for the combined data set, by year and sample type, and for domestic and nondomestic samples. Normal and outlier cannabis samples were determined based on the mean and SD of the $\Delta^9$-THC concentration for each year and sample type (40). Normal samples are defined as samples with potencies in the range: mean ± 2.5 × SD. Outlier samples are defined as samples with potencies that fall outside this range. The precision of the mean was determined through 95% confidence intervals (CIs). The CI was calculated using the Excel function TINV(probability, degrees of freedom), which returns the inverse or t-value of the Student's t-distribution as a function of the probability associated with the two-tailed Student's t-distribution and the degrees of freedom [number of samples ($n$) – 1]. The CI range is subsequently calculated as the mean ± the product of the TINV value and the standard error of the mean (SEM), i.e., the SD divided by the square root of the number of samples, thus mean ± SEM × TINV

[$SEM = SD/\sqrt{n}$, TINV = TINV(0.05, $n - 1$)]. A 95% CI is a range of values that contains the true mean of the population with 95% certainty. The Pearson product-moment correlation coefficient ($r$) was calculated using the Excel PEARSON function, and the standard error for the predicted mean values for each year in the regression was calculated using the Excel STEYX function.

## Results and Discussion

During the past 16 years (1993–2008), 46,211 samples of cannabis preparations confiscated in the United States, representing *c.* 8,321 tons, were analyzed at the University of Mississippi PM laboratory (Table 1). The PM program has analyzed 67,227 samples to date since 1968 (25–28). Samples classification is performed by the submitting agency and verified by the PM laboratory. Prior to 1995, there was no classification in the database for ditchweed; therefore, all ditchweed samples were classified as marijuana. However, interest in monitoring ditchweed samples and its effect on the overall potency of confiscated marijuana necessitated this category on the sample report form since 1995. The data presented in this report on ditchweed samples prior to 1995 were generated by retrospective review of the PM data. Marijuana samples with $\Delta^9$-THC <1% and CBD > $\Delta^9$-THC were classified as ditchweed. Cannabis, i.e., marijuana, sinsemilla, Thai sticks, and ditchweed, represents the overwhelming majority of the samples confiscated in the United States (98.7%), while the hashish and hash oil combined contribution is <1.5% (Table 1). Marijuana typically represents at least 50% of the samples. Sinsemilla samples gradually increased from 2002, with a concurrent decrease in the number of marijuana samples.

The yearly arithmetic mean $\Delta^9$-THC concentration for the different types of cannabis samples shows large variation within categories and over time, with only the ditchweed samples being relatively constant (Table 2). Hashish and hash oil sample potencies

TABLE 1—*Number of samples (*n*) analyzed by type and year.*

| | All | Marijuana* | | Sinsemilla* | | Thai sticks* | | Ditchweed* | | Hashish† | | Hash oil† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | *n* | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| 1993 | 3412 | 3033 | 88.9 | 123 | 3.6 | 0 | 0.0 | 200 | 5.9 | 39 | 1.1 | 17 | 0.5 |
| 1994 | 3327 | 3032 | 91.1 | 104 | 3.1 | 0 | 0.0 | 148 | 4.4 | 29 | 0.9 | 14 | 0.4 |
| 1995 | 4791 | 4430 | 92.5 | 164 | 3.4 | 2 | 0.04 | 163 | 3.4 | 19 | 0.4 | 13 | 0.3 |
| 1996 | 2455 | 2148 | 87.5 | 169 | 6.9 | 0 | 0.0 | 118 | 4.8 | 12 | 0.5 | 8 | 0.3 |
| 1997 | 2495 | 2273 | 91.1 | 121 | 4.8 | 0 | 0.0 | 60 | 2.4 | 31 | 1.2 | 10 | 0.4 |
| 1998 | 2283 | 2075 | 90.9 | 101 | 4.4 | 0 | 0.0 | 87 | 3.8 | 15 | 0.7 | 5 | 0.2 |
| 1999 | 2692 | 2450 | 91.0 | 136 | 5.1 | 0 | 0.0 | 72 | 2.7 | 23 | 0.9 | 11 | 0.4 |
| 2000 | 3148 | 2928 | 93.0 | 113 | 3.6 | 0 | 0.0 | 73 | 2.3 | 27 | 0.9 | 7 | 0.2 |
| 2001 | 2716 | 2398 | 88.3 | 235 | 8.7 | 0 | 0.0 | 63 | 2.3 | 13 | 0.5 | 7 | 0.3 |
| 2002 | 2413 | 1789 | 74.1 | 528 | 21.9 | 0 | 0.0 | 75 | 3.1 | 16 | 0.7 | 5 | 0.2 |
| 2003 | 2517 | 1893 | 75.2 | 538 | 21.4 | 0 | 0.0 | 66 | 2.6 | 16 | 0.6 | 4 | 0.2 |
| 2004 | 2637 | 1815 | 68.8 | 731 | 27.7 | 0 | 0.0 | 62 | 2.4 | 25 | 0.9 | 4 | 0.2 |
| 2005 | 3004 | 1964 | 65.4 | 931 | 31.0 | 0 | 0.0 | 56 | 1.9 | 47 | 1.6 | 6 | 0.2 |
| 2006 | 2890 | 1770 | 61.2 | 1032 | 35.7 | 0 | 0.0 | 53 | 1.8 | 32 | 1.1 | 3 | 0.1 |
| 2007 | 3097 | 1635 | 52.8 | 1327 | 42.8 | 0 | 0.0 | 47 | 1.5 | 70 | 2.3 | 18 | 0.6 |
| 2008 | 2334 | 1151 | 49.3 | 1093 | 46.8 | 0 | 0.0 | 28 | 1.2 | 50 | 2.1 | 12 | 0.5 |
| 1993–2008 | 46,211 | 36,784 | 79.6 | 7446 | 16.1 | 2 | 0.0 | 1371 | 3.0 | 464 | 1.0 | 144 | 0.3 |

*Total cannabis: 45,603 samples (98.7%).
†Total hashish + hash oil: 608 samples (1.3%).

TABLE 2—*Mean and SD $\Delta^9$-THC concentration by type of sample and year.*

| | All | | Marijuana | | Sinsemilla | | Thai sticks | | Ditchweed | | Hashish | | Hash oil | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| 1993 | 3.4 | 2.9 | 3.4 | 2.4 | 5.8 | 3.8 | 0.0 | 0.0 | 0.4 | 0.3 | 6.6 | 6.7 | 16.5 | 11.7 |
| 1994 | 3.5 | 2.5 | 3.5 | 2.1 | 7.5 | 4.8 | 0.0 | 0.0 | 0.4 | 0.3 | 4.6 | 3.6 | 11.6 | 7.9 |
| 1995 | 3.8 | 2.3 | 3.7 | 1.8 | 7.5 | 4.4 | 4.5 | 0.8 | 0.4 | 0.4 | 3.6 | 3.7 | 13.2 | 8.9 |
| 1996 | 4.1 | 3.0 | 3.9 | 2.2 | 9.2 | 4.7 | 0.0 | 0.0 | 0.4 | 0.3 | 2.5 | 1.4 | 12.8 | 9.5 |
| 1997 | 4.6 | 3.7 | 4.3 | 2.7 | 11.6 | 5.9 | 0.0 | 0.0 | 0.5 | 0.3 | 8.9 | 9.3 | 18.2 | 9.0 |
| 1998 | 4.5 | 3.6 | 4.2 | 2.9 | 12.3 | 5.2 | 0.0 | 0.0 | 0.4 | 0.3 | 5.9 | 5.2 | 15.8 | 9.9 |
| 1999 | 4.6 | 4.0 | 4.2 | 3.2 | 13.4 | 4.7 | 0.0 | 0.0 | 0.4 | 0.3 | 4.9 | 4.2 | 16.2 | 10.7 |
| 2000 | 4.9 | 4.0 | 4.7 | 3.4 | 12.8 | 4.4 | 0.0 | 0.0 | 0.4 | 0.3 | 4.2 | 4.2 | 28.6 | 11.6 |
| 2001 | 5.4 | 4.1 | 5.0 | 3.5 | 9.6 | 5.4 | 0.0 | 0.0 | 0.4 | 0.3 | 8.5 | 5.9 | 19.4 | 8.1 |
| 2002 | 6.4 | 5.1 | 5.1 | 3.4 | 11.4 | 5.7 | 0.0 | 0.0 | 0.4 | 0.3 | 9.1 | 8.5 | 22.5 | 28.3 |
| 2003 | 6.3 | 4.8 | 5.0 | 3.1 | 11.6 | 5.7 | 0.0 | 0.0 | 0.3 | 0.3 | 9.2 | 7.6 | 15.5 | 6.9 |
| 2004 | 7.2 | 5.8 | 5.4 | 3.6 | 11.9 | 6.0 | 0.0 | 0.0 | 0.4 | 0.3 | 18.9 | 15.1 | 31.3 | 34.6 |
| 2005 | 7.2 | 5.3 | 5.2 | 3.2 | 11.6 | 5.7 | 0.0 | 0.0 | 0.4 | 0.3 | 12.0 | 10.3 | 6.4 | 2.8 |
| 2006 | 7.8 | 6.5 | 5.6 | 4.0 | 11.2 | 6.5 | 0.0 | 0.0 | 0.3 | 0.2 | 29.3 | 19.7 | 18.7 | 26.1 |
| 2007 | 8.8 | 7.4 | 6.1 | 3.7 | 11.1 | 6.6 | 0.0 | 0.0 | 0.4 | 0.3 | 27.7 | 18.4 | 24.9 | 29.6 |
| 2008 | 8.8 | 6.9 | 5.8 | 3.9 | 11.5 | 6.2 | 0.0 | 0.0 | 0.4 | 0.3 | 23.1 | 19.6 | 6.5 | 9.7 |
| 1993–2008 | 5.6 | 5.0 | 4.5 | 3.1 | 11.1 | 6.1 | 4.5 | 0.8 | 0.4 | 0.3 | 14.1 | 15.7 | 16.8 | 16.3 |
| 95% CI range* | 5.53–5.62 | | 4.46–4.53 | | 11.01–11.28 | | 0.00–11.69 | | 0.37–0.40 | | 12.69–15.56 | | 14.07–19.45 | |

SD, Standard deviation.
*95% CI range: range of values that contains the true mean with 95% certainty.

showed the most variability over the 16-year period. The mean and SD for these categories were 14.1% ± 15.7% and 16.8% ± 16.3%, respectively. The marijuana $\Delta^9$-THC concentration appeared to gradually increase from 1993 to 2008, with a Pearson product-moment correlation coefficient ($r$) of 0.982 and a standard error for the predicted mean values of 0.17 (Fig. 1). The mean $\Delta^9$-THC concentration for sinsemilla fluctuated considerably, ranging from a minimum in 1993 (5.8% ± 3.8%) to a maximum in 1999 (13.4% ± 4.7%) (Table 2, Fig. 1). Other than the expected finding that the yearly mean potencies of sinsemilla samples were much higher than that for marijuana samples, there did not appear to be any meaningful trend in the mean potency of the sinsemilla samples. The mean $\Delta^9$-THC concentration of sinsemilla samples between 1993 and 2000 increased from 5.8% to 12.8% (121.8% increase), dropping slightly in 2001 (9.6%), and stabilizing between 2002 and 2008 (11.5% ± 0.3%) (Fig. 1).

The change in cannabis potency over the past 40 years has been the subject of much debate and controversy. This report investigates the influence of outlier samples on the overall mean concentration of $\Delta^9$-THC for the time period studied in an attempt to clarify this issue. Normal and outlier cannabis preparations are samples with $\Delta^9$-THC concentrations that fall within and outside the range mean ± 2.5 × SD, respectively.

The outlier samples for marijuana and sinsemilla represent 2.4% and 0.5%, respectively, of the total samples for each type (Table 3). The distribution of $\Delta^9$-THC concentrations is positively skewed,

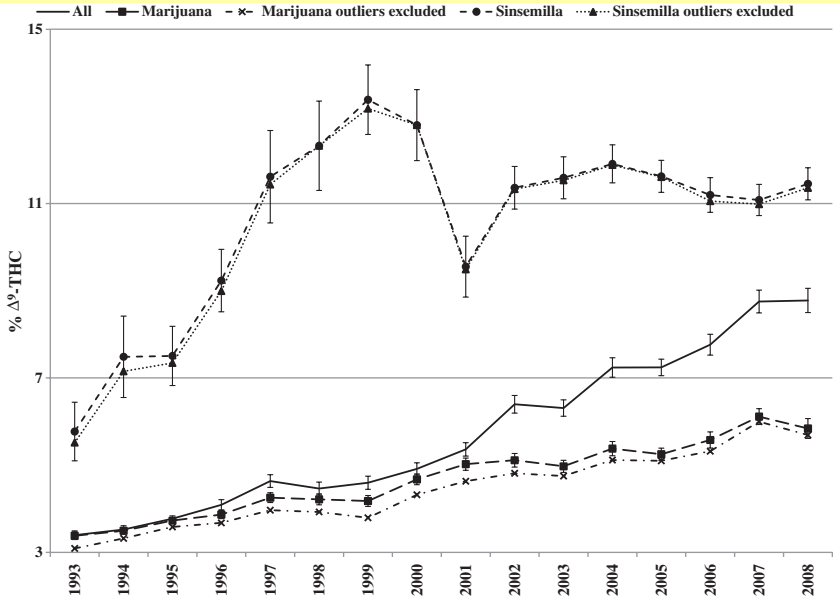


FIG. 1—*Mean $\Delta^9$-THC concentration with 95% confidence intervals for all samples, marijuana and sinsemilla samples, and marijuana and sinsemilla samples with outliers excluded.*

TABLE 3—*Mean and SD $\Delta^9$-THC concentration for marijuana and sinsemilla samples with outliers* excluded.*

| | Marijuana | | | | | Sinsemilla | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Outliers | All samples | | Outliers excluded | | Outliers | All samples | | Outliers excluded | |
| Year | % | Mean | SD | Mean | SD | % | Mean | SD | Mean | SD |
| 1993 | 2.9 | 3.4 | 2.4 | 3.1 | 1.7 | 2.4 | 5.8 | 3.8 | 5.5 | 3.4 |
| 1994 | 2.3 | 3.5 | 2.1 | 3.3 | 1.7 | 1.9 | 7.5 | 4.8 | 7.2 | 4.2 |
| 1995 | 2.0 | 3.7 | 1.8 | 3.6 | 1.5 | 1.2 | 7.5 | 4.4 | 7.3 | 4.2 |
| 1996 | 2.3 | 3.9 | 2.2 | 3.7 | 1.8 | 1.8 | 9.2 | 4.7 | 9.0 | 4.4 |
| 1997 | 3.1 | 4.3 | 2.7 | 4.0 | 2.2 | 0.8 | 11.6 | 5.9 | 11.4 | 5.6 |
| 1998 | 2.7 | 4.2 | 2.9 | 3.9 | 2.3 | 0.0 | 12.3 | 5.2 | 12.3 | 5.2 |
| 1999 | 3.5 | 4.2 | 3.2 | 3.8 | 2.4 | 1.5 | 13.4 | 4.7 | 13.2 | 4.4 |
| 2000 | 3.2 | 4.7 | 3.4 | 4.3 | 2.8 | 0.0 | 12.8 | 4.4 | 12.8 | 4.4 |
| 2001 | 3.4 | 5.0 | 3.5 | 4.6 | 2.8 | 0.4 | 9.6 | 5.4 | 9.5 | 5.4 |
| 2002 | 2.5 | 5.1 | 3.4 | 4.8 | 2.8 | 0.2 | 11.4 | 5.7 | 11.3 | 5.7 |
| 2003 | 2.1 | 5.0 | 3.1 | 4.8 | 2.7 | 0.4 | 11.6 | 5.7 | 11.5 | 5.6 |
| 2004 | 2.1 | 5.4 | 3.6 | 5.1 | 3.1 | 0.1 | 11.9 | 6.0 | 11.9 | 6.0 |
| 2005 | 1.5 | 5.2 | 3.2 | 5.1 | 3.0 | 0.1 | 11.6 | 5.7 | 11.6 | 5.7 |
| 2006 | 2.0 | 5.6 | 4.0 | 5.3 | 3.5 | 0.8 | 11.2 | 6.5 | 11.1 | 6.3 |
| 2007 | 0.9 | 6.1 | 3.7 | 6.0 | 3.5 | 0.5 | 11.1 | 6.6 | 11.0 | 6.5 |
| 2008 | 1.1 | 5.8 | 3.9 | 5.7 | 3.7 | 0.5 | 11.5 | 6.2 | 11.4 | 6.1 |
| 1993–2008 | 2.4 | 4.5 | 3.1 | 4.2 | 2.7 | 0.5 | 11.1 | 6.1 | 11.1 | 6.0 |
| 95% CI range† | – | 4.46–4.53 | | 4.22–4.27 | | – | 11.01–11.28 | | 10.92–11.20 | |

SD, Standard deviation.
*Mean – 2.5 × SD > Outlier > Mean + 2.5 × SD.
†95% CI range: range of values that contains the true mean with 95% certainty.

i.e., all outliers are samples with potencies higher than the mean potency. It is therefore important that the potential effect of the outliers is examined to determine whether the apparent trend of increasing potency is real or simply a statistical artifact. A comparison of the mean potency of marijuana and sinsemilla samples calculated for all samples versus for samples with outliers excluded indicates that the mean $\Delta^9$-THC concentration decreases for each year when the outliers are excluded (Table 3, Fig. 1). However, the general pattern of increasing potency of marijuana samples since 1993 appears to exist even when outliers are excluded. The Pearson product-moment correlation coefficient (*r*) and standard error for the predicted mean values after exclusion of marijuana sample outliers were 0.981 and 0.18, respectively. Because of the greater variability found in the potency of sinsemilla samples, fewer cases were excluded as outliers and thus there was little effect on the mean potency for each of the years reported (Table 3, Fig. 1). The mean $\Delta^9$-THC concentration for marijuana and sinsemilla samples decreased by 0.24% and 0.08%, respectively, after exclusion of the outliers.

Further evidence that the mean $\Delta^9$-THC concentration for marijuana may be increasing is inferred by the analysis of the percentage of samples each year with $\Delta^9$-THC concentration more than 3%, 5%, and 9%. Marijuana samples with $\Delta^9$-THC >9% increased from 3.23% (1993) to a maximum 21.47% (2007). Conversely, the number of marijuana sample containing $\Delta^9$-THC <3% decreased between 1993 and 2007, with a slight increase in 2008 (Fig. 2). The trend for sinsemilla samples with $\Delta^9$-THC >9% followed a similar pattern to the overall trend for the yearly mean potencies

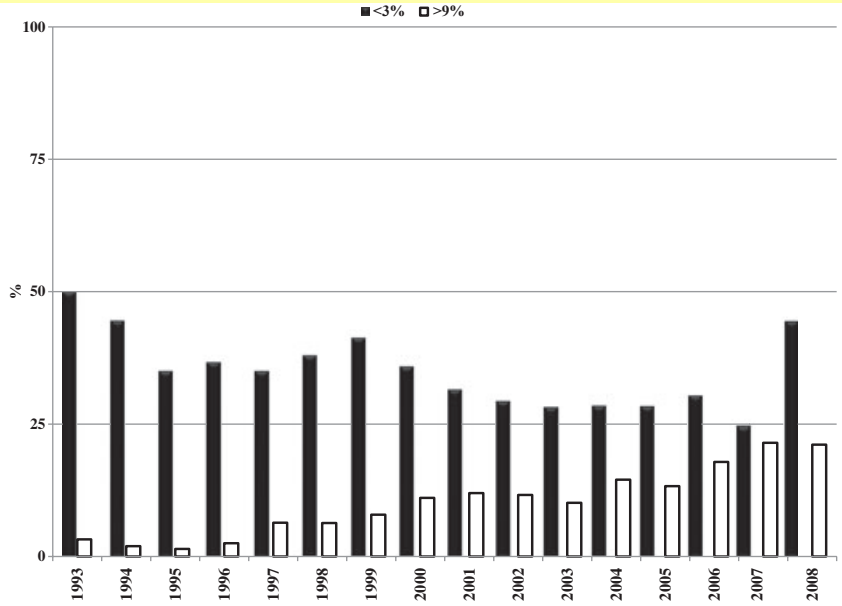


FIG. 2—*Prevalence of low (<3%) and high (>9%) potency marijuana samples.*

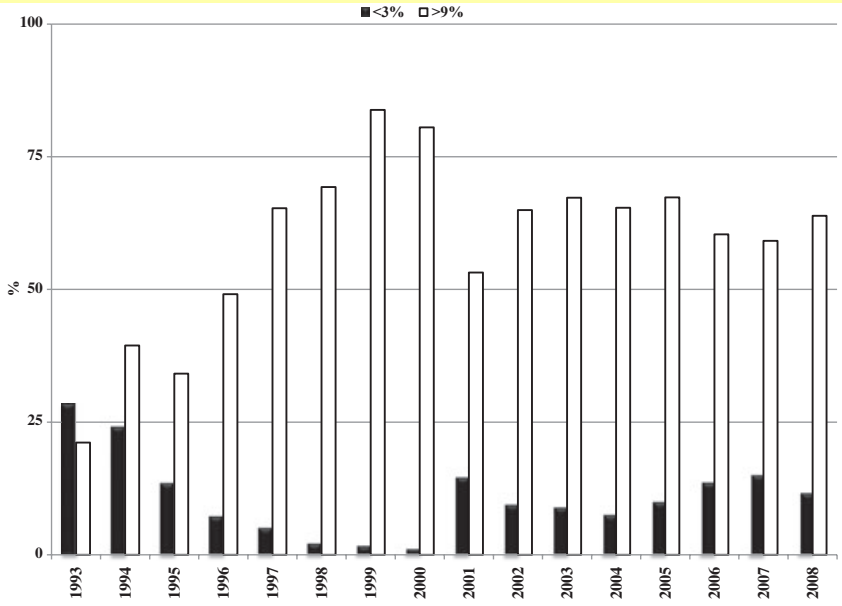


FIG. 3—*Prevalence of low (<3%) and high (>9%) potency sinsemilla samples.*

(Figs 1 and 3). Considering the large number of cannabis samples analyzed each year, it is doubtful that these observations are statistical artifacts.

The overall number of samples, mean, SD, maximum and minimum concentrations of $\Delta^9$-THC for the different types of samples categorized by origin, i.e., domestic or nondomestic, indicates that ditchweed is mainly a domestic product, whereas Thai sticks, hashish, and hash oil are nondomestic products (Table 4). Marijuana and sinsemilla samples represent more than 95% of all seizures. It is important to mention that samples are classified as being of domestic origin only if the seizure is made from a growing operation (indoor or outdoor) within the United States. All other samples are classified as being nondomestic, although they could possibly have been produced in the United States prior to seizure. It is also important to note that all nondomestic sample seizures made by the DEA are of final products produced from mature plant material. In contrast, the domestic samples provided by the state eradication programs are seized at different stages of plant maturity. Overall, the number of samples of known domestic origin represents approximately one-third of all samples confiscated. The number of nondomestic seizures was consistently higher when compared to that of domestic seizures (Fig. 4). The mean $\Delta^9$-THC concentration for nondomestic cannabis samples showed a gradual increase, while domestic samples had little fluctuation (Fig. 5).

The mean concentration of the minor cannabinoids CBC, CBD, CBN, CBG, and THCV were also monitored (Table 5). CBD is the major cannabinoid found in ditchweed and is present in elevated amounts in intermediate type cannabis (moderate levels of both $\Delta^9$-THC and CBD) used to make hashish. The cannabinoid content of hashish and hash oil samples shows that, while hashish

TABLE 4—*Number of samples (*n*), mean, SD, maximum and minimum $\Delta^9$-THC concentration by origin and type of sample.*

| Origin | Type | *n* | Mean | SD | Maximum | Minimum |
|---|---|---|---|---|---|---|
| Domestic | Marijuana | 10,308 | 3.0 | 2.8 | 24.7 | <0.01 |
| | Sinsemilla | 3067 | 7.9 | 5.5 | 33.1 | 0.1 |
| | Thai sticks | 0 | – | – | – | – |
| | Ditchweed | 1257 | 0.4 | 0.3 | 2.4 | <0.01 |
| | Hashish | 3 | 34.0 | 25.4 | 52.9 | 5.1 |
| | Hash oil | 2 | 0.2 | 0.01 | 0.23 | 0.21 |
| | 1993–2008 | 14,637 | 3.8 | 4.1 | 52.9 | <0.01 |
| Nondomestic | Marijuana | 26,476 | 5.1 | 3.0 | 37.2 | <0.01 |
| | Sinsemilla | 4379 | 13.4 | 5.4 | 32.3 | 0.5 |
| | Thai sticks | 2 | 4.5 | 0.8 | 5.1 | 4.0 |
| | Ditchweed | 114 | 0.4 | 0.3 | 1.2 | 0.1 |
| | Hashish | 461 | 14.0 | 15.6 | 66.3 | <0.01 |
| | Hash oil | 142 | 17.0 | 16.3 | 81.7 | <0.01 |
| | 1993–2008 | 31,574 | 6.4 | 5.1 | 81.7 | <0.01 |
| All Samples | Marijuana | 36,784 | 4.5 | 3.1 | 37.2 | <0.01 |
| | Sinsemilla | 7446 | 11.1 | 6.1 | 33.1 | 0.1 |
| | Thai sticks | 2 | 4.5 | 0.8 | 5.1 | 4.0 |
| | Ditchweed | 1371 | 0.4 | 0.3 | 2.4 | <0.01 |
| | Hashish | 464 | 14.1 | 15.7 | 66.3 | <0.01 |
| | Hash oil | 144 | 16.8 | 16.3 | 81.7 | <0.01 |
| | 1993–2008 | 46,211 | 5.6 | 5.0 | 81.7 | <0.01 |

SD, Standard deviation.

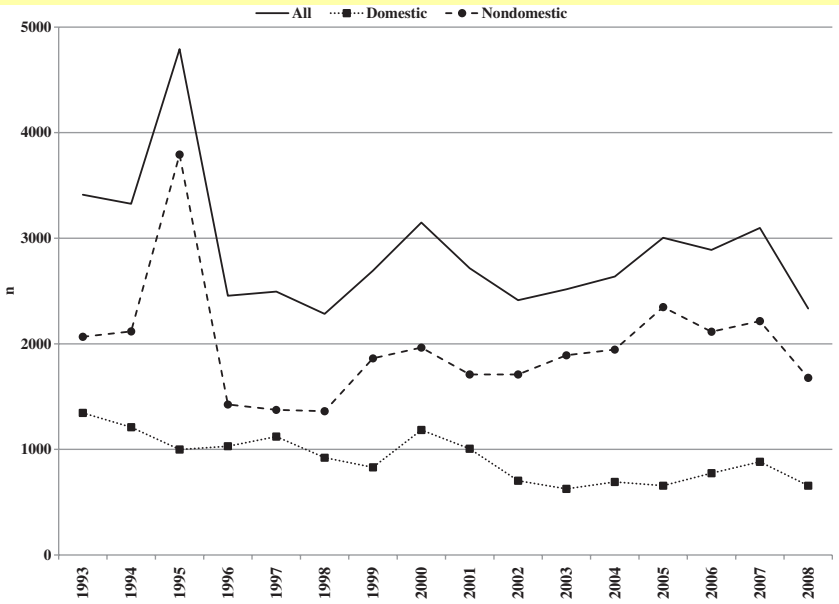


FIG. 4—*Number (*n*) of domestic and nondomestic samples.*

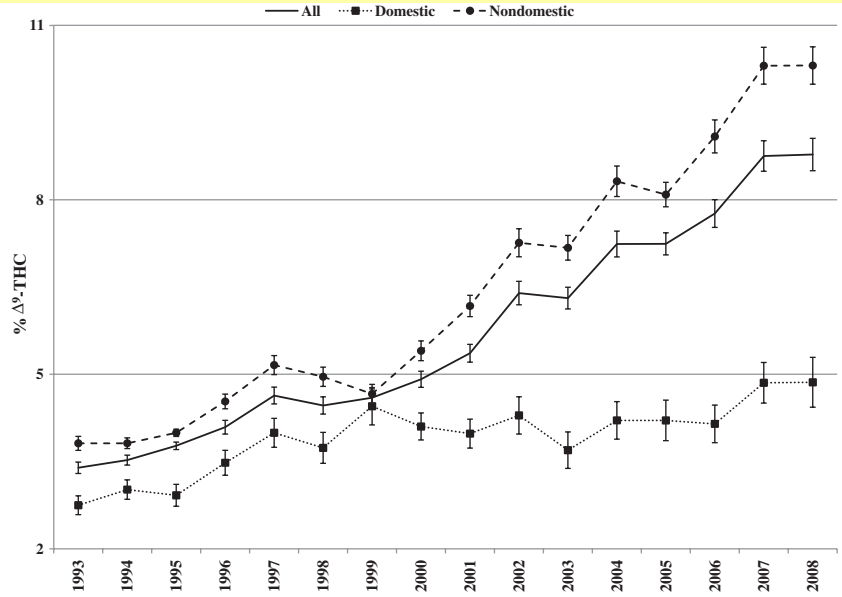


FIG. 5—*$\Delta^9$-THC concentration of domestic and nondomestic samples with 95% confidence intervals.*

TABLE 5—*Mean concentration of minor cannabinoids by type and year.*

| | All | | | | | | Marijuana | | | | | | Sinsemilla | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | THC | CBC | CBD | CBN | CBG | THCV | THC | CBC | CBD | CBN | CBG | THCV | THC | CBC | CBD | CBN | CBG | THCV |
| 1993 | 3.4 | 0.2 | 0.3 | 0.3 | 0.0 | 0.0 | 3.4 | 0.2 | 0.2 | 0.3 | 0.0 | 0.0 | 5.8 | 0.2 | 0.2 | 0.0 | 0.1 | 0.0 |
| 1994 | 3.5 | 0.2 | 0.4 | 0.2 | 0.1 | 0.1 | 3.5 | 0.2 | 0.3 | 0.2 | 0.1 | 0.1 | 7.5 | 0.2 | 0.5 | 0.1 | 0.3 | 0.1 |
| 1995 | 3.8 | 0.2 | 0.3 | 0.3 | 0.1 | 0.0 | 3.7 | 0.2 | 0.3 | 0.3 | 0.1 | 0.0 | 7.5 | 0.3 | 0.3 | 0.1 | 0.3 | 0.1 |
| 1996 | 4.1 | 0.2 | 0.4 | 0.3 | 0.2 | 0.1 | 3.9 | 0.2 | 0.3 | 0.2 | 0.1 | 0.1 | 9.2 | 0.3 | 0.5 | 0.1 | 0.4 | 0.1 |
| 1997 | 4.6 | 0.3 | 0.4 | 0.2 | 0.2 | 0.1 | 4.3 | 0.3 | 0.4 | 0.2 | 0.2 | 0.1 | 11.6 | 0.3 | 0.4 | 0.1 | 0.5 | 0.1 |
| 1998 | 4.5 | 0.2 | 0.4 | 0.3 | 0.2 | 0.1 | 4.2 | 0.2 | 0.3 | 0.2 | 0.1 | 0.1 | 12.3 | 0.4 | 0.4 | 0.2 | 0.5 | 0.1 |
| 1999 | 4.6 | 0.2 | 0.4 | 0.4 | 0.2 | 0.0 | 4.2 | 0.2 | 0.4 | 0.4 | 0.2 | 0.0 | 13.4 | 0.3 | 0.3 | 0.2 | 0.5 | 0.1 |
| 2000 | 4.9 | 0.2 | 0.5 | 0.4 | 0.2 | 0.1 | 4.7 | 0.2 | 0.4 | 0.4 | 0.2 | 0.1 | 12.8 | 0.2 | 0.3 | 0.2 | 0.4 | 0.1 |
| 2001 | 5.4 | 0.2 | 0.5 | 0.3 | 0.3 | 0.1 | 5.0 | 0.2 | 0.5 | 0.3 | 0.2 | 0.1 | 9.6 | 0.2 | 0.3 | 0.2 | 0.4 | 0.1 |
| 2002 | 6.4 | 0.2 | 0.4 | 0.2 | 0.2 | 0.1 | 5.1 | 0.2 | 0.5 | 0.2 | 0.2 | 0.1 | 11.4 | 0.3 | 0.2 | 0.2 | 0.3 | 0.1 |
| 2003 | 6.3 | 0.2 | 0.5 | 0.2 | 0.3 | 0.1 | 5.0 | 0.2 | 0.5 | 0.3 | 0.3 | 0.1 | 11.6 | 0.3 | 0.3 | 0.2 | 0.4 | 0.1 |
| 2004 | 7.2 | 0.3 | 0.5 | 0.3 | 0.3 | 0.1 | 5.4 | 0.2 | 0.5 | 0.3 | 0.3 | 0.1 | 11.9 | 0.3 | 0.2 | 0.2 | 0.5 | 0.1 |
| 2005 | 7.2 | 0.3 | 0.5 | 0.3 | 0.4 | 0.1 | 5.2 | 0.3 | 0.5 | 0.4 | 0.3 | 0.1 | 11.6 | 0.3 | 0.2 | 0.2 | 0.4 | 0.1 |
| 2006 | 7.8 | 0.2 | 0.4 | 0.3 | 0.3 | 0.1 | 5.6 | 0.2 | 0.5 | 0.3 | 0.3 | 0.1 | 11.2 | 0.3 | 0.2 | 0.2 | 0.4 | 0.1 |
| 2007 | 8.8 | 0.3 | 0.4 | 0.3 | 0.4 | 0.1 | 6.1 | 0.2 | 0.5 | 0.3 | 0.3 | 0.1 | 11.1 | 0.3 | 0.3 | 0.2 | 0.4 | 0.1 |
| 2008 | 8.8 | 0.3 | 0.4 | 0.3 | 0.4 | 0.1 | 5.8 | 0.2 | 0.4 | 0.3 | 0.3 | 0.1 | 11.5 | 0.3 | 0.2 | 0.2 | 0.4 | 0.1 |
| 1993–2008 | 5.6 | 0.2 | 0.4 | 0.3 | 0.2 | 0.1 | 4.5 | 0.2 | 0.4 | 0.3 | 0.2 | 0.1 | 11.1 | 0.3 | 0.2 | 0.2 | 0.4 | 0.1 |
| SD | 5.0 | 0.3 | 0.9 | 0.5 | 0.3 | 0.1 | 3.1 | 0.2 | 0.7 | 0.4 | 0.3 | 0.1 | 6.1 | 0.4 | 0.9 | 0.3 | 0.4 | 0.1 |

| | Ditchweed | | | | | | Hashish | | | | | | Hash oil | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | THC | CBC | CBD | CBN | CBG | THCV | THC | CBC | CBD | CBN | CBG | THCV | THC | CBC | CBD | CBN | CBG | THCV |
| 1993 | 0.4 | 0.1 | 1.7 | 0.0 | 0.0 | 0.0 | 6.6 | 0.7 | 3.8 | 2.3 | 0.5 | 0.3 | 16.5 | 0.7 | 0.1 | 7.7 | 0.3 | 0.5 |
| 1994 | 0.4 | 0.1 | 2.0 | 0.0 | 0.0 | 0.0 | 4.6 | 0.5 | 3.5 | 1.7 | 0.5 | 0.2 | 11.6 | 0.6 | 0.2 | 3.1 | 0.4 | 0.5 |
| 1995 | 0.4 | 0.1 | 1.6 | 0.0 | 0.1 | 0.0 | 3.6 | 0.5 | 3.3 | 1.7 | 0.3 | 0.1 | 13.2 | 1.0 | 0.7 | 4.2 | 0.5 | 0.3 |
| 1996 | 0.4 | 0.1 | 2.1 | 0.0 | 0.1 | 0.0 | 2.5 | 0.7 | 4.5 | 2.4 | 0.3 | 0.1 | 12.8 | 1.1 | 1.3 | 4.0 | 0.5 | 0.5 |
| 1997 | 0.5 | 0.1 | 1.9 | 0.0 | 0.0 | 0.0 | 8.9 | 0.7 | 4.0 | 2.1 | 0.5 | 0.3 | 18.2 | 1.0 | 0.3 | 3.5 | 0.3 | 0.6 |
| 1998 | 0.4 | 0.2 | 2.0 | 0.0 | 0.0 | 0.0 | 5.9 | 0.8 | 1.7 | 2.0 | 0.3 | 0.2 | 15.8 | 0.8 | 0.2 | 3.6 | 0.2 | 0.5 |
| 1999 | 0.4 | 0.1 | 1.8 | 0.1 | 0.1 | 0.0 | 4.9 | 0.6 | 1.8 | 2.1 | 0.5 | 0.3 | 16.2 | 1.3 | 0.4 | 4.8 | 0.3 | 0.4 |
| 2000 | 0.4 | 0.1 | 2.0 | 0.0 | 0.0 | 0.0 | 4.2 | 0.6 | 4.9 | 2.3 | 0.4 | 0.1 | 28.6 | 1.6 | 0.5 | 1.7 | 0.9 | 0.7 |
| 2001 | 0.4 | 0.1 | 1.8 | 0.0 | 0.1 | 0.0 | 8.5 | 0.6 | 2.7 | 1.5 | 0.6 | 0.3 | 19.4 | 1.2 | 1.3 | 4.4 | 0.9 | 0.6 |
| 2002 | 0.4 | 0.1 | 1.5 | 0.0 | 0.0 | 0.0 | 9.1 | 0.6 | 2.5 | 1.4 | 0.4 | 0.2 | 22.5 | 0.5 | 0.3 | 1.7 | 1.2 | 0.3 |
| 2003 | 0.3 | 0.1 | 1.8 | 0.1 | 0.1 | 0.0 | 9.2 | 0.7 | 3.9 | 1.8 | 0.4 | 0.2 | 15.5 | 0.8 | 0.2 | 1.3 | 0.3 | 0.4 |
| 2004 | 0.4 | 0.1 | 1.5 | 0.1 | 0.1 | 0.0 | 18.9 | 0.7 | 0.8 | 1.4 | 0.7 | 0.2 | 31.3 | 1.1 | 1.1 | 2.2 | 1.2 | 0.4 |
| 2005 | 0.4 | 0.1 | 1.9 | 0.1 | 0.1 | 0.0 | 12.0 | 0.9 | 1.7 | 1.9 | 0.4 | 0.2 | 6.4 | 0.2 | 0.3 | 1.1 | 0.2 | 0.2 |
| 2006 | 0.3 | 0.1 | 2.4 | 0.2 | 0.1 | 0.0 | 29.3 | 0.7 | 1.6 | 1.3 | 0.8 | 0.2 | 18.7 | 0.4 | 0.1 | 0.6 | 0.4 | 0.1 |
| 2007 | 0.4 | 0.1 | 2.0 | 0.1 | 0.1 | 0.0 | 27.7 | 0.8 | 1.2 | 1.8 | 1.0 | 0.3 | 24.9 | 0.9 | 0.6 | 1.5 | 0.7 | 0.3 |
| 2008 | 0.4 | 0.2 | 1.9 | 0.0 | 0.1 | 0.0 | 23.1 | 0.9 | 2.1 | 2.1 | 0.9 | 0.4 | 6.5 | 0.3 | 0.2 | 0.8 | 0.2 | 0.1 |
| 1993–2008 | 0.4 | 0.1 | 1.8 | 0.0 | 0.0 | 0.0 | 14.1 | 0.7 | 2.5 | 1.9 | 0.6 | 0.3 | 16.8 | 0.9 | 0.5 | 3.3 | 0.5 | 0.4 |
| SD | 0.3 | 0.1 | 1.5 | 0.2 | 0.1 | 0.0 | 15.7 | 0.7 | 2.9 | 1.4 | 0.6 | 0.3 | 16.3 | 0.9 | 0.8 | 3.8 | 0.7 | 0.4 |

CBC, cannabichromene; CBD, cannabidiol; CBG, cannabigerol; CBN, cannabinol; $\Delta^9$-THC, $\Delta^9$-tetrahydrocannabinol; THCV, tetrahydrocannabivarin.

is prepared from intermediate type cannabis, hash oil is prepared from drug-type cannabis (high $\Delta^9$-THC and low CBD levels) (3–6,16). CBC and CBN are usually higher in hashish and hash oil samples compared to cannabis samples. The CBN concentration relative to $\Delta^9$-THC reflects the age of the samples (41). CBG content is typically about 3–5% of the $\Delta^9$-THC content; however, in ditchweed this ratio increases to more than 10%, even though this type of cannabis preparation has the lowest overall mean CBG content. This is because ditchweed has very low $\Delta^9$-THC content (0.4% ± 0.3%). THCV, an important biomarker in cannabis (42,43), is generally present at about 0.5–2.5% of the $\Delta^9$-THC content.

## Conclusions

The question over the increase in potency of cannabis is complex and has evoked many opinions. The issue has been clouded somewhat by reports of 10- and 30-fold increases in cannabis potency since the 1970s. It is however clear that cannabis has changed during the past four decades. It is now possible to mass produce plants with potencies inconceivable when concerted monitoring efforts started 40 years ago. The PM program has strived to answer this cannabis potency question, while realizing that the data collected in this and other programs have some scientific and statistical shortcomings. These include randomness of samples, correctly identifying the various cannabis products, sampling, natural degradation of $\Delta^9$-THC over time, and different analytical techniques, making comparing results between countries and over time very difficult. However, analysis of the available data in conjunction with the PM program results makes a strong case that cannabis is not only more potent than in the past but also that this high-potency product's market share is also growing. This is clearly evident in the increase in sinsemilla seizures and in the increase in marijuana and sinsemilla samples with $\Delta^9$-THC >9%. The question now becomes: What are the effects of the availability of high-potency products on cannabis users?

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XLR-11 was temporarily made a Schedule I substance by the DEA's emergency scheduling power in May 2013. 78 Fed. Reg. 23735 (May 16, 2013). Shortly before the two-year temporary period was scheduled to expire in May 2015, the temporary scheduling of XLR-11 was extended for an additional year, and the DEA moved to have XLR-11 placed permanently onto the Controlled Substances List. 80 Fed. Reg. 27611 (May 14, 2015); 21 U.S.C. § 811(h)(2). As of this date, XLR-11 is still temporarily scheduled under Schedule I. 21 C.F.R. § 1308.11.

## II. Sentencing Guidelines

### a. Drug Equivalency [2]

The sentencing issue presented in this case is that XLR-11 is not listed in either the Drug Quantity Table or Drug Equivalency table of § 2D 1.1 of the Guidelines.

When determining the base offense level for a controlled substance not listed in the Guidelines, a court should use "the marihuana equivalency of the most closely related controlled substance referenced in this guideline." 18 U.S.C. § 2D1.1, Application Note 6. In determining the most closely related substance, a court should consider, "to the extent practicable":

> *(A) Whether the Controlled Substance not referenced in this guideline has a chemical structure that is substantially similar to a controlled substance referenced in this guideline.*
>
> *(B) Whether the controlled substance not referenced in this guideline has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance referenced in this guideline.*
>
> *(C) Whether a lesser or greater quantity of the controlled substance not referenced in this*

> *guideline is needed to produce a substantially similar effect on the central nervous system as a controlled substance referenced in this guideline.*

*Id.*

To determine the "most closely related controlled substance" to XLR-11, I held a hearing on December 11, 2015. At that time, the Government presented testimony from Dr. Jordan Trecki, a pharmacologist with the DEA. The Government argued, with the support of Dr. Trecki, that XLR-11 is most closely related to the controlled substance tetrahydrocannabinol ("THC"). THC is commonly known as the psychoactive ingredient in marijuana.

Hossain presented testimony from Dr. Nicholas Vito Cozzi, a pharmacologist and professor at the University of Wisconsin School of Medicine and Public Health, and Dr. Gregory Dudley, a chemist and a professor at Florida State University. Hossain argued, with the support of Dr. Dudley, that marijuana is the most closely related referenced controlled substance to XLR-11. Additionally, both Doctors Cozzi and Dudley took issue with Dr. Trecki's characterization of THC as the most closely related controlled substance to XLR-11, explaining the flaws in the research that Dr. Trecki relied upon in coming to his conclusions.

Based on the testimony and exhibits presented, I will address each of the Section 2D 1.1 factors in turn.

Factor A—Substantial Similarity: All three experts agreed that, with regards to the first factor, that the chemical structure of XLR-11 is not similar to either marijuana or THC.

Factor B—Efficacy: The second factor to consider is whether the effect of XL11 is substantially similar to the effect of a referenced controlled substance. Dr. Trecki testified that the pharmacological effects of XLR-11 are most similar to THC. (DE 229, Tr. at 29). He explained that synthetic cannabinoids, like XLR-11, activate the

CB1 receptor in the brain, which is the receptor responsible for the psychoactive properties of cannabinoids. (DE 229, Tr. at 67).

Dr. Trecki also testified about the results of a drug discrimination study, which he explained demonstrated that THC and XLR-11 were similar in effect:

> *This is a study where you evaluate animals, where you give them the specific — the test drug, for example THC, and they learn a specific behavior. You then switch out the THC [for another drug] and you observe the behavior . . . So for example, in this case . . . [when animals were given XLR-11] the animals could not differentiate between XLR-11 and the THC.*

(DE 229, Tr. at 68).

Dr. Trecki also compared XLR-11 to THC, explaining that because both XLR-11 and THC are single chemicals, unlike marijuana, XLR-11 is more closely related to THC than marijuana:

> *The marijuana plant, as noted in many published peer review publications, has between 80 and 100 separate cannabinoids in the plant. It has between 500 and 800 different chemicals that make up a living organism in the plant called marijuana. When you look at drugs like XLR-11 . . . these are single manmade chemicals applied to inert, nonpsychoactive vegetable material.*

(DE 229, Tr. at 36).

Finally, Dr. Trecki testified that "the hallucinogenic effects of XLR-11 on the central nervous system are substantially similar to THC." (DE 229, Tr. at 69).

Hossain's experts, Doctors Cozzi and Dudley, both challenged Dr. Trecki's conclusion, and testified that the pharmacological effects of XLR-11 were not necessarily analogous to THC. Dr. Cozzi explained that there were problems with Dr. Trecki's drug discrimination study

that purportedly demonstrates that XLR-11 and THC are similar in effect. Dr. Cozzi opined that the sample size of rodents in the study was smaller than he typically relied on with confidence, and that the results were not reproducible. (DE 229, Tr. at 98, 103).

Further, Dr. Dudley distinguished XLR-11 from THC in effect. He testified that, although XLR-11 binds to the CB1 receptor, as Dr. Trecki had testified, XLR-11 appears to bind more strongly to the CB2 receptor, which is not considered the "psychoactive receptor":

> *A: XLR-11 binds more tightly, more strongly to the CB2 receptor than to the CB1 receptor.*
>
> *Q: In other words, more tightly to the one that would modulate pain as opposed to the one that gets you high; is that a way to say it?*
>
> *A: . . . [T]he one that's primarily located outside of the central nervous system that is not associated with getting you high . . .*

(DE 229, Tr. at 183).

Dr. Dudley further testified that he believes XLR-11 is most closely related to marijuana in effect:

> *Q: When people use marijuana and they get high, they are getting high because the THC?*
>
> *A: That's the consensus, yes.*
>
> *Q: . . . [B]ut marijuana, of course, is separately listed as a schedule one drug, correct?*
>
> *A: Yes.*
>
> *Q: And is marijuana then, in your opinion, appropriate or inappropriate to do the comparison with XLR-11?*
>
> *A: Given that one must choose one of the substances from the guidelines, I think marijuana is appropriate.*

(DE 229, Tr. at 188-89).

Factor C—Potency: The third factor to consider is

whether a lesser or greater amount of XLR-11 is needed to produce a substantially similar effect on the central nervous system as the most closely related referenced substance.

Dr. Trecki testified that a lesser amount of XLR-11 is needed to produce the effects of THC because "XLR acts in an increased manner" over THC. (DE 229, Tr. at 69). In fact, Dr. Trecki testified that, in one study, XLR-11 was "approximately four times as potent as THC." (DE 229, Tr. at 74).

Dr. Cozzi testified that he did not think one could make conclusions about XL11 potency in humans based on studies done on rodents because ". . . the [in] vivo animal studies are not reliable predictors of what a drug will produce in a human being." (DE 229, Tr. at 105). Further, he objected that the data relied on by Dr. Trecki is highly variable and is not reproducible. (DE 229, Tr. at 18). Dr. Dudley similarly testified that there was nothing in the literature that would support finding the XLR-1 l's potency is similar to THC. (DE 229, Tr. at 119).

Based on the testimony I heard on, I find that XLR-11 cannot be easily analogized to THC or to marijuana. While XLR-11 appears to have some of the same psychoactive effects as THC, the chemical structure is unique. The testimony from the experts on the second two factors—efficacy and potency—conflicts. However, because I am instructed by the Guidelines to choose a related substance, I am most persuaded by Dr. Trecki's testimony that the referenced controlled substance XLR-11 most closely relates to is THC. XLR-11, like THC, acts on the CB1 receptor, was found to be similar to THC in one drug discrimination study, and, like THC, is a single chemical,

## b. Guideline Range

Once I have determined the most closely related controlled substance referenced in the Guidelines, the

Guidelines instruct that I should use the marijuana equivalency of the related substance to determine the base offense level.

According to the Drug Equivalency Table, the conversion ratio of THC to marijuana is 167:1. Thus, for the purposes of the Guidelines calculation, one gram of marijuana is equal to 167 grams of THC. The amount of XLR-11 that the Government attributes to Hossain, which Hossain did not dispute at the sentencing hearing, was 216 kilograms. Therefore, using the Drug Equivalency Table, Hossain is responsible for 36,072 kilograms of marijuana. This makes Hossain's base offense level 36. (DE 205 at ¶149).

The presentence investigation report filed as to Hossain calculates that Hossain should have eight offense points added to the base offense level: two offense points added pursuant to § 2D1.1(b)(12), another two points added pursuant to § 2D1.1(b)(15)(C), and four points added pursuant to § 3B1.1(a). Hossain also had three points detracted, pursuant to § 3E1.1(a) and § 3E1.1(b). (DE 205 at ¶¶ 50, 51, 53, 57, 58). At the sentencing hearing, I found that Hossain should have an adjustment for role in the offense, but that the adjustment should only be two points, pursuant to § 3B 1.1(c).

Accordingly, Hossain's adjusted offense level is 39, his criminal history category is I, and his resulting Guidelines range is 262 to 327 months of imprisonment.

## III. Variance

Although the federal sentencing statute requires that I give consideration to the Guidelines, the sentence should be tailored in light of other concerns. *See Kimbrough v. United States*, 552 U.S. 85 (2007); *United States v. Booker*, 543 U.S. 220 (2005). After *Booker*, there is no presumption that the Guideline sentence should apply, and a variance from the advisory Guidelines may not be presumed unreasonable. *See Rita v. U.S.*, 551 U.S. 338, 351, 354-55 (2007). "A district

judge must include the Guidelines range in the array of factors warranting consideration. The judge may determine, however, that, in the particular case, a within-Guidelines sentence is greater than necessary to serve the objectives of sentencing." *Kimbrough*, 552 U.S. at 91 (internal quotations omitted).

In the context of the crack-cocaine disparity, the Supreme Court in *Kimbrough* upheld a district court's decision to not apply the 100:1 crack-cocaine ratio when the ratio resulted in a sentence that was "greater than necessary" in light of the § 3553(a) factors. *Kimbrough*, 552 U.S. at 92. In fact, the Supreme Court has gone so far as to say in *Spears v. United States* that *Kimbrough* recognized a "district courts' authority to vary from the crack cocaine Guidelines based on *policy* disagreements with them . . ." 555 U.S. 261, 264 (2009). These cases rely on the *post-Booker* discretion of the district court to consider § 3553(a) and vary from the advisory Guidelines when the Guidelines do not fit the instant crime.

Accordingly, I will, and must, consider the § 3553(a) factors in determining whether a Guidelines sentence serves the objectives of sentencing. Factors I should consider under § 3553(a) include: the nature and circumstances of the offense, the history and characteristics of the defendant, and the need for the sentence to provide just punishment, deterrence, incapacitation, and rehabilitation. 18 U.S.C. § 3553(a)(2).

Clearly, this is a serious offense. A 2012 study showed that eleven percent of high school seniors had used synthetic cannabinoids. A recent 2015 study from the same group shows that the number of high school seniors using synthetic cannabinoids had dropped to five percent. *See* Press Release, University of Michigan, Monitoring the Future, "Use of ecstasy, heroin, synthetic marijuana, alcohol, cigarettes declined amount US teens in 2015" (December 16, 2015). This speaks to the need to deter individuals from dealing in these drugs; although on the decline, synthetic cannabinoids

were once relatively commonplace among high schoolers, and dealers should be deterred from distributing these chemicals so that the numbers do not rise again.

According to the DEA's rulemaking in May 2015, there has only been one death tied to XLR-11. 80 Fed. Reg. 27611 (May 14, 2015). However, there have still been increased reports in harm from synthetic cannabinoids more generally and, because the information on synthetic cannabinoids is limited, considering synthetic cannabinoids together may give a more complete picture of the dangers and effects of these drugs. The Government submitted to the Court several articles that discuss case studies of individuals exhibiting complications after they have ingested some type of synthetic cannabinoid. A common trend of these articles shows that individuals who have been hospitalized following synthetic cannabinoid use present kidney injury. *See* DE 217-2, Letter to the Editor from Doctors of Emergency Medicine; DE 217-4, "Acute Kidney Injury Associated with Synthetic Cannabinoid Use—Multiple States, 2012," Morbidity and Mortality Weekly, February 15, 2013.

However, despite the potential dangers of synthetic cannabinoids, and the clear need for deterrence, I believe the Guidelines range for the instant offense fails to achieve the goals of sentencing.

For starters, I am not convinced that THC is a particularly relevant substitute for XLR-11. Based off of the testimony I heard, I believe synthetic cannabinoids need their own category in the Drug Equivalency Chart in order to account for the differences between XLR-11 and THC. But, in the absence of an amendment to the Guidelines, I will use the THC Guideline range as a starting point.

In considering the THC to marijuana ratio, I find it troubling that there does not seem to be any reason behind the 1:167 ratio. Although I asked each of the experts at the hearing, no one could provide me with a

reason for this ratio, which has major implications in determining the base level offense. After my own research and a phone call to the Sentencing Commission, I still could find no basis for this ratio. It appears to have been included in the first set of Guidelines in 1987, with no published explanation. While a sentence must reflect the seriousness of the offense to provide just punishment, a sentence based on a range that seems to have no cognizable basis is not just.

At the hearing, I heard testimony from Dr. Cozzi regarding a more appropriate ratio for THC to marijuana:

> *[S]aying that one gram of THC is equal to 167 grams of marijuana is like saying 167 grams of marijuana contains a gram of THC. That's what equivalence means. But if you calculate what percentage of THC that is on the weight, you take the one [and] divide it by 167, you get 0.6. So 0.6 percent of the total weight [of the marijuana] is THC. That's completely unrealistic in terms of psychoactive marijuana. We know from Government studies that the average THC content in marijuana today is over 14 percent. So the ratio should be one to seven, not one to 167.*

(DE 229, Tr. at 116-17).

I find this ratio to be better founded than the 1:167 ratio that no one could explain, as it reflects the actual amount of THC in marijuana today. Although I will not rewrite the Guidelines and apply this ratio for THC, this lower ratio is persuasive as to why the current Guideline range fails to provide just punishment for this offense. If I were to use a 1:7 ratio, the amount of XLR-11 Hossain's charged with—216 kilograms—would be equivalent to 1,512 kilograms of marijuana. This would make his base offense level 30 under the Guidelines. When including the adjustments for Hossain's offense level, discussed *supra*, Hossain's sentence range—using an offense level of 33 and a criminal history category of

I—would be 135 to 168 months.

This sentence range is more reasonable than the sentence that the Government suggests I impose, based off the 1:167 ratio. The Government's proposed sentence would mean Hossain starts at the same base offense level as a dealer distributing 167 times more marijuana, a dealer or distributor of 30 to 90 kilograms of heroin, or a dealer or distributor of 150 to 450 kilograms of cocaine. This hardly seems to account for the relative dangers of this crime. Crack cocaine offenses are twice as likely to involve a gun than marijuana offenses. *See* Drug Offenders in Federal Prison: Estimate of Characteristics based on Linked Data, Bureau of Justice Statistics, October 2015. Further, the relative harm from use of XLR-11 does not reach the level of harm from overdoses of cocaine or heroin. As stated previously, the DEA report only lists one known death due to XLR-11. [3] In contrast, in 2014 there were 5,415 reported deaths from cocaine in the United States. *See* "Overdose Death Rates," National Institute of Drug Abuse, December 2015. That same year there were 10,574 reported deaths from heroin in the United States. *Id.*

Additionally, I find the newness of the regulation of XLR-11, as well as the infancy of our understanding of the effects of XLR-11 and other synthetic cannabinoids, to be relevant to determining Hossain's sentence. XLR-11 was first temporarily scheduled in May 2013. In January 2015, Hossain told DEA agents that in 2012, prior to XLR-11 being scheduled, he worked at his father's store where synthetic cannabinoids were sold. Hossain also stated that in May or June of 2012 Hossain and his wife began working at a warehouse that packaged these drugs. All of this conduct occurred prior to XLR-11 being temporarily scheduled and—at least initially—Hossain was unlikely to appreciate the seriousness of his conduct.

Although Hossain was eventually put on notice that XLR-11 was illegal, I find it relevant to Hossain's culpability that XLR-11 was intended to serve as a

replacement for marijuana. Due to the relative infancy of knowledge about synthetic cannabinoids, and XLR-11 in particular, it is unlikely that Hossain or his co-defendants knew the dangers of the synthetic cannabinoids when they were engaged in the instant conduct. If Hossain thought this substance was like marijuana, because it created a high similar to marijuana, he likely believed it posed no more danger than marijuana. Furthermore, Hossain was unlikely to be aware that the substance was, in fact, more dangerous and more severely punished than marijuana. In 2013, the average sentence length of marijuana traffickers was 39 months. *See* Quick Facts: Marijuana Trafficking Offenses, United States Sentencing Commission, 2013. In this case, had I treated XLR-11 as marijuana, Hossain would have been subjected to a sentence of 70 to 87 months.

While I don't find that marijuana is the appropriate substance to compare XLR-11 to—due to the testimony and articles presented about the dangers of XLR-11—I do believe it is relevant when considering whether Hossain appreciated the dangers of the drug with which he was importing. I find that the goals of sentencing, particularly punishment and deterrence, are not achieved by sentencing Hossain to upwards of thirty years in prison for dealing in a substance that was intended to mimic marijuana and so new that only a few years before his arrest it was being sold in gas stations and convenience stores.

Additionally, in considering the other § 3553 factors, I find persuasive that Hossain had no prior criminal history and the instant offense was non-violent.

## IV. Conclusion

Although THC is the closest controlled substance to XLR-11 that is currently referenced in the Guidelines, I do not find the Guidelines range for THC particularly helpful in calculating Hossain's sentence. The Guidelines Range yields a sentence that is "greater than

necessary" to achieve § 3553(a)'s purpose. I am dissuaded from sentencing Hossain within the Guideline range because not one expert could provide any scientific basis for the 1:167 ratio for comparing marijuana to THC. Additionally, the nature of this offense, particularly the newness of the regulation of this drug, persuades me that varying downward is necessary. Furthermore, Hossain's lack of any criminal history persuades me that a within-Guidelines range would be "greater than necessary" to achieve any sentencing goals.

Accordingly, for reasons stated in this memorandum and in open court, I sentence Saiful Hossain to 120 months imprisonment, to be followed by three years of supervised release.

DONE AND ORDERED.

## FootNotes

1. Other names for synthetic cannabinoids include "K2" and "Spice," which were names given to specific versions of early synthetic cannabinoids. Synthetic cannabinoids are also sometimes referred to as "synthetic marijuana." I use the term "synthetic cannabinoids" to refer generally to these drugs that are used to mimic the high from marijuana.

2. As stated in open court on January 5, 2016, the following Drug Equivalency analysis— as well as my § 3553(a) analysis that relies on a discussion XLR-11—also applies to my sentences of Hossain's co-defendants, Ahmed Maher Elhelw and Ahmed Yehia Khalifa.

3. While Dr. Trecki testified regarding other deaths related to synthetic cannabinoids, it is unclear how many deaths there have been and whether the chemicals present in those cases are similar to XLR-11.

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## Comment

*Leagle.com reserves the right to edit or remove comments but is under no obligation to do so, or to explain individual moderation decisions.*

# EXHIBIT 4

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE WESTERN DISTRICT OF LOUISIANA**
**LAFAYETTE DIVISION**

| | | |
|---|---|---|
| UNITED STATES OF AMERICA<br><br>Plaintiff,<br><br>v.<br><br>THOMAS WILLIAM MALONE, JR.<br><br>Defendant. | : | Case No.: 6:12-CR-00146-EEF-PJH |

DECLARATION OF NICHOLAS V. COZZI, Ph.D.

I. My name is Nicholas Vito Cozzi. I am currently a scientist and educator in the Department of Cell and Regenerative Biology at the University of Wisconsin School of Medicine and Public Health in Madison, WI. I hold a B.S. degree in Pharmacology and Toxicology and a Ph.D. degree in Pharmacology from the University of Wisconsin School of Pharmacy. I teach Medical Pharmacology to second-year medical students and I teach various courses in Pharmacology and Toxicology to undergraduate students, M.D. and Ph.D. students, pharmacy students, and veterinary students.

II. I have approximately 29 years of research experience in the design, chemical synthesis, and pharmacological testing of novel compounds. My research involves the design, chemical synthesis, and pharmacological testing of substances with central nervous system activity, especially those with psychostimulant, hallucinogenic, and antidepressant effects. My laboratory is interested in how these agents act in the brain to affect awareness, cognition, and mood, and in their clinical value for treating addiction, anxiety, depression, post-traumatic fear, and other mental health ailments. I have published the results of my research in international peer-reviewed scientific journals beginning in 1991 and continuing through the present. My qualifications and experience are detailed in my curriculum vitae, which is attached.

III. I have been asked to comment on certain statements made by Jordan Trecki, Ph.D., a pharmacologist employed by the Drug Enforcement Administration, regarding the compound known as AM-2201*, and render my own opinions on AM-2201. In particular, my comments relate to written and oral testimony given by Dr. Trecki in the sentencing hearing in the United States District Court for the District of Minnesota in U.S. v. Carlson (Case #12-CR-305).

* AM-2201 is identified as (1-(5-fluoropentyl)-3-(1-naphthoyl)indole).

IV. It is Dr. Trecki's opinion that 1) AM-2201 is pharmacologically "most closely related" to delta 9-tetrahydrocannabinol (THC) and 2) "AM2201 is at least as potent, if not more potent than THC, supporting a potency ratio of 1:1." Dr. Tecki's makes the following statements to support his opinion.

A. Dr. Trecki: "AM2201 has a hallucinogenic effect on the central nervous system that is substantially similar to THC."

1. Neither AM-2201 nor THC is accurately described as a "hallucinogen" under any current scientific or medical classification scheme.

i. It is widely held among pharmacologists, medical doctors, and other professionals that the term "hallucinogen" refers to drugs whose primary effects resemble the effects produced by mescaline, psilocybin, and lysergic acid diethylamide (LSD); another term for these substances is "psychedelic" (Nichols, 2004). No pharmacologist or medical professional, or even the casual user, would claim that THC mimics the effects of LSD. There is no evidence that AM-2201 does so either.

ii. Many drugs can produce hallucinations as a side-effect in some individuals. For example, the Attention Deficit Hyperactivity Disorder drug amphetamine (Adderall®), the anti-Parkinson's disease drugs levodopa (Larodopa®) and pramipexole (Mirapex®), and the anti-HIV drug efavirenz (Sustiva®) can produce hallucinations at normal, recommended doses. However, none of these drugs are correctly classified as "hallucinogens".

2. No systematic studies are available in the scientific literature that qualify or quantify the psychoactive effects of AM-2201 in humans either by itself or in comparison to THC.

i. A controlled metabolic study in which a single volunteer consumed an oral dose of 5 mg AM-2201 reported no physical or mental effects at any stage of the experiment, even though the substance was detectable in the blood and urine (Hutter et al., 2013). In contrast, oral doses of THC as low as 2.5 mg are associated with a variety of physical and psychotropic effects such as dry mouth, reddening of the eyes, euphoria, dizziness, memory impairment, analgesia, and sleepiness, among others (http://www.rxabbvie.com/pdf/marinol_PI.pdf). At a minimum, these data suggest that THC is at least 2-fold more potent than AM-2201 when taken orally, but it is likely that the oral potency ratio of THC to AM-2201 is much higher.

ii. The lack of psychoactivity of oral AM-2201 is very likely due to extensive metabolism in the gastrointestinal tract and liver, a phenomenon known as the "first-pass" effect.

iii. There are no study data available that describe the effect or potency of AM-2201 when administered by any other routes. Some other potential routes of ingestion include inhalation of vaporized or aerosolized material, sublingual absorption, intravenous or intramuscular injection, or transdermal absorption.

iv. There exist numerous literature reports of subjects in whom varying levels of AM-2201 was detected *post hoc* (e.g., following a traffic stop) (Alhadi et al., 2013; Kronstrand et al., 2013; Rodrigues et al., 2013; Yeakel and Logan, 2013; Elian and Hackett, 2014; Kim et al., 2014; Musshoff et al., 2014). However, it is not possible to establish a dose-related effect of AM-2201 from these reports because the routes of administration are unknown, no uniform sample collection times were adhered to, and the levels of AM-2201 detected in these persons varied by over 400-fold.

v. Because "potency" refers to the size of a dose or the concentration of a drug required to produce a specific effect, and because there are no studies establishing a specific dose-related effect of AM-2201, it is erroneous to make the assertion that AM-2201 "is at least as potent, if not more potent than THC," as claimed by Dr. Trecki.

vi. It is certain, at least, that any psychoactive or physiological effects produced by AM-2201 are highly dependent on the route of administration, with oral doses being completely inactive, whereas oral doses of THC are fully active. Thus, any potency comparison between AM-2201 and THC that does not take into account the route of administration is faulty.

B. Dr. Trecki: "Data from *in vitro* receptor binding studies demonstrate that both AM2201 and THC bind to the cannabinoid 1 (CB1) receptor."

1. It is well known that data from *in vitro* binding experiments are not sufficient to conclude what effect, if any, a substance will have in humans.

2. The fact that two substances bind to the same receptor does not indicate that they will have similar biological effects. For example, the substances acetylcholine and atropine have very different biological effects, even though they both bind to the same (muscarinic) receptor.

3. An ingested drug substance must reach its site of action in the body in sufficient quantity or concentration to produce a pharmacological effect; all drugs exhibit a threshold concentration below which they are inactive.

4. *In vitro* binding experiments are conducted in isolated cell or tissue preparations. They are intentionally designed to exclude biological processes such as absorption, distribution, metabolism, and excretion (collectively known as *pharmacokinetics*). These processes determine the quantity and concentration of a substance reaching a

biological target, for example, brain tissue. Thus, pharmacokinetic processes govern whether a drug will attain the minimum threshold required to produce a psychoactive effect or a physiological response.

5. The absence of any physical or psychotropic effect when 5 mg AM-2201 was ingested by mouth (Hutter et al., 2013) is a case in point in demonstrating the importance of the pharmacokinetic processes described above in determining the ultimate effects (or lack thereof) of a drug; the fact that oral AM-2201 is inactive demonstrates the limitations of relying on binding data to reach conclusions regarding the activity of a drug. If one disregards human pharmacokinetic processes, one will reach an erroneous conclusion regarding the activity and potency of AM-2201.

6. Therefore, while *in vitro* binding experiments can yield useful information about biological drug targets, they are not designed to answer, and cannot establish, whether a substance will have a biological effect at all, the nature of its effect, or whether the substance will reach its site of action in sufficient quantity or concentration to produce a response. One cannot conclude from *in vitro* binding data that a compound will produce a response in a human being.

C. Dr. Trecki: "Data from *in vitro* functional assays demonstrate that both AM2201 and THC activate CB1 receptors and thus act as agonists at the CB1 receptor. Agonist activation of the CB1 receptor leads to psychoactive and physiological actions."

1. Here, Dr Trecki tries to draw a conclusion regarding psychological and physiological responses (which can *only* occur in an intact animal) from *in vitro* data. Again, it is well known that data from *in vitro* assays do not allow one to conclude what effect, if any, a substance will have in an intact organism. As discussed above, an ingested substance must reach its site of action in sufficient quantity or concentration to produce a behavioral effect. This information is simply unobtainable from an *in vitro* assay.

2. *In vitro* functional assays typically measure biochemical or electrophysiological phenomena while deliberately excluding pharmacokinetic processes. These processes determine whether or not a drug will have an observable effect. Without considering pharmacokinetic processes, it is erroneous to draw any conclusions regarding the supposed psychological or physiological activity of a drug in an intact human being.

3. Thousands of compounds are known which show functional agonist activity *in vitro*, only to be shown later to be completely inert in humans. Hence, Dr. Trecki's conclusion that "Agonist activation of the CB1 receptor leads to psychoactive and physiological actions" is erroneous and premature. The observation of functional activity in an *in vitro* study may allow one to formulate hypotheses about biological or psychological effects in humans, but these conjectures must ultimately be tested by experiment.

4. The biochemical signaling cascades, which are studied in *in vitro* functional assays, are not understood well enough to predict specific psychoactive effects.

5. *In vitro* functional assays, like *in vitro* binding assays, are not designed to answer, and cannot establish, whether a substance will have a biological or psychological effect at all, the nature of its effect, or whether the substance will reach its site of action in sufficient quantity or concentration to produce an observable response. One cannot draw a conclusion about whole-person responses from *in vitro* data.

D. Dr. Trecki: "Data from *in vivo* studies (drug discrimination tests) demonstrate that AM2201 has subjective effects that that are substantially similar to the effects of THC."

1. Despite an exhaustive search of the peer-reviewed scientific literature, including sources such as PubMed, MedLine, and the Library of Congress, no drug discrimination studies were found to support Dr. Trecki's statement. There are no scientific or medical publications comparing the subjective effects of AM-2201 to those of THC.

   i. Here, it appears that Dr. Trecki refers to *unpublished* data obtained from Dr. Michael Forster and Dr. Michael Gatch from the University North Texas, which he used in oral testimony at the sentencing hearing in the United States District Court for the District of Minnesota in U.S. v. Carlson (Case # 12-CR-305). In his testimony, Dr. Trecki admits that none of the drug discrimination studies that he relies on have been published in the scientific literature.

   ii. Dr. Trecki contends that "The results of the drug discrimination assays, they have been peer reviewed. The researchers at the University of Texas that originally did the research peer reviewed their own work." It appears that Dr. Trecki does not fully comprehend the meaning of the phrase "peer review". By definition, peer review is an evaluation conducted by *peers* (i.e., other experts), not oneself. The whole point of peer review is to obtain an *anonymous*, *independent* critique and evaluation of one's work—it is not scientifically acceptable to claim that scientists "peer reviewed their own work". This critical step in the scientific publication process is meant to ensure that the experimental methods and resulting data are sound and that the conclusions are supported by the experimental results, thereby lending credence to the study.

   iii. Both Drs. Forster and Gatch are well-respected scientists with experience and publications in the areas of behavioral pharmacology, including drug discrimination. Nonetheless, their drug discrimination work on AM-2201 has yet to be validated through the peer review process. It is scientifically unacceptable to cite unpublished work until other scientists with the expertise to critique the studies have validated it.

2. While there exists much literature showing that drug discrimination studies in animals can indeed separate drugs into classes which have similar effects in humans, including drugs with THC-like effects, there are important exceptions and limits to the drug discrimination approach. Rat drug discrimination tests are not always reliable.

    i. Data from animal drug discrimination assays may produce "false positives" regarding subjective effects in humans. For example, the drugs lisuride, quipazine, and yohimbine are three drugs that are known NOT to be hallucinogenic in humans. However, these three drugs substitute for the hallucinogen LSD in rat drug discrimination assays (Appel et al., 2004). Thus, drug discrimination assays conducted in nonhuman animal subjects can lead to erroneous conclusions. False positive results cast doubt on the reliability of such assays to predict whether the "subjective effects" of two drugs in animals "are substantially similar" to drug effects, if any, produced in human beings.

    ii. Likewise, while discriminative stimulus effects of THC often exhibit a high degree of pharmacological specificity, there is not always a correspondence between THC-like stimulus effects in rats and a drug's ability to produce a THC-like intoxication in humans.

        a. Drugs that produce psychoactive effects that are unlike THC in humans can nevertheless produce THC-like responses in rats. For example, MDMA, diazepam, and pentobarbital partially or fully substitute for THC in animal drug discrimination tests (Mokler et al., 1986; Barrett et al., 1995). These drugs are not perceived to be THC by human beings.

        b. On the other hand, some compounds that are known to produce THC-like effects in humans fail to substitute for THC in rats (Hollister, 1974; Balster and Prescott, 1992).

E. In his testimony in U.S. v. Carlson, Dr. Trecki states "In the absence of human data, it would be inappropriate to administer these type of drugs to human patients for the reasons of there are no accepted medical uses for these drugs in the United States."

1. Dr. Trecki is misinformed. There are numerous ongoing clinical trials involving natural and synthetic cannabinoids presently occurring in the United States and elsewhere around the world. Accepted medical uses are *only* determined through clinical testing in humans. In fact, laws enacted by the Congress of the United States *require* drug testing in humans to assess safety and efficacy before a drug can be approved for clinical use. This testing is regulated and reviewed by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, whose mission is to ensure that drugs marketed in the United States are safe and effective.

2. Dr. Trecki states "In addition, the adverse effects experienced by multiple people as reported in either case reports or poison control centers demonstrate that this would not be appropriate to give to a human. There's no medical purpose for it, and the adverse effects are quite serious."

    a. There are numerous medical purposes for which natural or synthetic cannabinoids are being developed (Pacher et al., 2006) and there are literally hundreds of ongoing or completed clinical trials involving these substances. Some of these FDA- and DEA-approved studies include clinical trials for anticancer activity, antiemetic effects, appetite stimulation, analgesia, antianxiety effects, insomnia, antiseizure activity, inflammatory bowel disease, multiple sclerosis, fibromyalgia, obesity, and many other psychological and physical ailments. *See* www.clinicaltrials.gov, a Web site maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) for a listing.

    b. All currently FDA-approved drugs can produce adverse effects; the potential of a substance to produce adverse effects in no way precludes clinical trials with that substance.

F. Dr. Trecki claims: "AM2201 has a potency ratio of 1:1 with THC that is based upon data demonstrating that AM2201 is at least as potent (≥) as THC."

1. "Potency" refers to the size of a dose or the concentration of a drug required to produce a specific effect. The statement by Dr. Trecki does not indicate exactly what drug effect is being measured nor does he provide any data used to calculate the "potency ratio".

V. According to the sentencing documents in U.S. v. Carlson, AM-2201 has been made equivalent to JW-018 (identified as [1-pentyl-3-(1-naphthoyl)indole]), which is then made equivalent to THC for sentencing purposes.

A. I have been unable to locate any published studies that compare the potency of AM-2201 to JW-018.

B. According to the U.S.S.C. § 2D1.1, n.8(D), 1 gram of THC, whether synthetic or organic, is made equivalent to 167 grams of marihuana.

1. The THC content calculated by this guideline and expressed as a THC percent = 1/167 x 100 = 0.6%. Marihuana with a THC percent of less than 1% is called "ditchweed" or "hemp" and is used for manufacturing (e.g., hemp cloth, hemp rope) or in the food industry (e.g., hemp seed oil, hemp protein) (Holler et al., 2008).

C. The 1:167 multiplier does not accurately reflect the actual THC content of contemporary marijuana that is used for medicinal or psychoactive purposes. The multiplier artificially inflates the severity of a punishment by using an implausibly low marijuana THC content.

1. The National Institute on Drug Abuse maintains a marijuana Potency Monitoring Program directed by Dr. Mahmoud A. ElSohly at the National Center for Natural Products Research at the University of Mississippi School of Pharmacy, University, MS. This program provides analytical potency data for marijuana seized in the United States.

2. According to the Potency Monitoring Program test results, marihuana cultivated for psychoactive effects had a THC content in the 3.4-5.8% in 1993. The THC content increased to over 14.5% by 2013. (Mehmedic et al., 2010; Botticelli, 2014).

3. Therefore the sentencing guideline *miscalculates* the actual THC content of present-day marihuana by about 24-fold (14.5/0.6), resulting in a **multiplier that is at least 24-fold too high**. The multiplier, adjusted for actual present-day THC content, would be about 1:7, not 1:167.

VI. Summary

A. Dr. Trecki's conclusions about AM-2201 are based on extrapolations from *in vitro* experiments and unvetted animal data. Such data are not accepted by the scientific community to be a sufficient basis from which to draw conclusions regarding drug responses in human beings. In fact, over 90% of potential new drugs are not approved by the FDA for human use, in large part because of the failure of *in vitro* and animal testing to reliably predict drug effects in humans (DiMasi et al., 2003). At best, Dr. Trecki's speculations could form the basis of a hypothesis that could then be rigorously tested in humans with the proper safeguards in place.

B. The 1:167 sentencing multiplier appears to be arbitrary and capricious. It is not based on the actual THC content of today's pharmacologically active marijuana.

Recoverable Signature

X

Nicholas Vito Cozzi, Ph.D.

Signed by: Nicholas V. Cozzi

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## EDUCATION

**Ph.D., Pharmacology** **1994**
University of Wisconsin-Madison School of Pharmacy
Doctoral Thesis: *Pharmacological Studies of Some Psychoactive Phenylalkylamines: Entactogens, Hallucinogens, and Anorectics*

**B.S., Pharmacology and Toxicology** **1988**
University of Wisconsin-Madison School of Pharmacy

## AWARDS AND GRANTS

Neuropharmacology Research Grant, Usona Institute **2011 – Present**

Wisconsin Medical Alumni Association Distinguished Basic Science Teaching Award **2013**

University of Wisconsin Professional Development Grant **2008 – 2009**

National Institute on Drug Abuse Grant DA017675 **2004 – 2007**

Brody Basic Science Incentive Award, Brody School of Medicine, East Carolina University **2001 – 2002**

Excellence in Teaching Award, Brody School of Medicine, East Carolina University **2000**

Brain and Behavior Research Foundation (formerly NARSAD) Young Investigator Award **1997 – 2000**

## TEACHING EXPERIENCE

**Visiting Professor: Human Services 1130 (undergraduate course)** **2011 – Present**
College of DuPage, Glen Ellyn, IL
Topic: Molecular and cellular mechanisms of psychedelic drug action

**Lecturer: Molecular Principles in Pharmacology (graduate course)** **2011 – 2013**
University of Wisconsin School of Medicine and Public Health, Madison, WI
Topics: General principles, drug disposition, autonomic and neuromuscular drugs, central nervous system agents, autacoid pharmacology

**Course Director, Lecturer: Medical Pharmacology (Foundations of Medicine 1-4; professional/graduate courses)** **2007 – Present**
University of Wisconsin School of Medicine and Public Health, Madison, WI
Topics: General principles, drug disposition, autonomic and neuromuscular drugs, cardiovascular and blood drugs, central nervous system agents, gastrointestinal drugs, chemotherapeutics, autacoid pharmacology, endocrine drugs, botanicals, toxicology, immunopharmacology, therapeutic drug monitoring, drug interactions

**Lecturer: Laboratory Techniques in Pharmacology and Toxicology (graduate course)** **2007 – Present**
University of Wisconsin School of Pharmacy, Madison, WI
Topic: Pharmacology of neurotransmitter uptake transporters

**Visiting Professor: Foundations of Psychedelic Studies (undergraduate course)** **1986 – Present**
Northern Illinois University, DeKalb, IL
Topic: Pharmacology of psychedelic agents

**Lecturer: Basic and Clinical Veterinary Therapeutics (professional course)** **2009**
University of Wisconsin School of Veterinary Medicine, Madison, WI
Topics: Pharmacotherapy of pancreatic, adrenal, and thyroid disorders

**Course Director, Lecturer: Physiology in Pharmacology (graduate course)** **2008 – 2011**
University of Wisconsin School of Medicine and Public Health, Madison, WI
Topics: Homeostasis, cell structure, movement across membranes, neuronal signaling, sensory physiology, brain, muscle, endocrine, reproduction, cardiovascular system, pulmonary, renal, gastrointestinal, metabolism, immunology

**Course Director, Lecturer: Pharmacology (professional course)** **2005 – 2007**
Carroll University, Waukesha, WI
Topics: General principles, drug disposition, autonomic and neuromuscular drugs, cardiovascular and blood drugs, central nervous system drugs, gastrointestinal drugs, chemotherapeutics, autacoid pharmacology, endocrine drugs, botanicals, toxicology, drug interactions

**Lecturer: Physiological Proteogenomics (graduate course)** **2003 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topic: Applications of proteome analysis to drug development and toxicology

**Course Director, Lecturer: Pharmacology Seminar (graduate course)** **2001 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

**Lecturer: Molecular Pharmacology (graduate course)** **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Receptor kinases, neurotransmitter transporters, cell adhesion molecules, site-directed mutagenesis, chimeras, positron emission tomography

**Course Director, Lecturer: Laboratory Research Techniques (graduate course)** **2000 - 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Neurotransmitter transporter assays, cell culture techniques, polymerase chain reaction

**Lecturer: Central Nervous System Pharmacology (graduate course)** **1999 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Neurotransmitter receptors, gene knockouts, synaptic vesicle storage and release mechanisms

**Lecturer: Cellular and Molecular Neuroscience (graduate course)** **1999 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Neurotransmitter receptors, neurotransmitter transporters

**Lecturer: Medical Pharmacology (professional/graduate course)** **1998 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: General principles, receptor mechanisms, dose-response relationships, absorption, distribution, metabolism, excretion, pharmacokinetics, drug interactions

**Lecturer: Pharmacology (professional course)** **1995 – 1998**
University of Wisconsin School of Pharmacy, Madison, WI
Topic: Cardiovascular pharmacology

**Lecturer: Environmental Toxicology (graduate course)** **1994 – 1998**
Center for Environmental Toxicology, University of Wisconsin-Madison, Madison, WI
Topics: Neurotoxicology, gastrointestinal toxicology

**Teaching Assistant: Pharmacy curriculum (various undergraduate Pharmacy courses)** **1989 – 1994**
University of Wisconsin School of Pharmacy, Madison, WI

**Graduate Students**
Dr. LuAnn Cuthbertson-Lucas; received Ph.D. 2001
Dr. Kevin Foley; received Ph.D. 2002
Dr. Kevin DeSanty; received Ph.D. 2002
Dr. Jessica Gaskey-Sharpe; received Ph.D. 2004

## PUBLICATIONS

**Refereed**

JS Bonano, ML Banks, R Kolanos, F Sakloth, M Barnier, RA Glennon, **NV Cozzi**, JS Partilla, MH Baumann, SS Negus. Abuse-related neurochemical and behavioral effects of para-substituted methcathinone analogs in rats. I. Quantitative structure-activity relationship (QSAR) analysis. *Brit. J. Pharmacol., (submitted)*

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MH Baumann, JS Partilla, KR Lehner, EB Thorndike, AF Hoffman, M Holy, RB Rothman, SR Goldberg, CR Lupica, HH Sitte, SD Brandt, SR Tella, **NV Cozzi**, CW Schindler. Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive “bath salts” products. *Neuropsychopharmacology, 38*, 552-562 (2013)

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C Leckie, BE McKay, **NV Cozzi**, PE Mallet. Candidate for abuse: acute effects of the "bath salts" constituent 4-methylmethcathinone (mephedrone, 4-MMC). *Southern Ontario Neurosci. Assoc. Abs., 33*, A23, 33rd Annual Conference, Wilfrid Laurier University, Waterloo ON, N2L 3C5 (2013)

KR Lehner, JS Partilla, MA Ayestas Jr., **NV Cozzi**, MH Baumann. Differential effects of “bath salts” constituents, methylone and MDPV, on monoamine transporter function. *Soc. Neurosci. Abs., 38*, 667.18 (2012)

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DM Raffel, W Chen, DL Gildersleeve, YW Jung, **NV Cozzi**. Transport of [$^{11}$C]meta-hydroxyephedrine, [$^{11}$C]-epinephrine, and biogenic amines by the human norepinephrine transporter. *J. Nucl. Med., 45*, 216P (2004)

**NV Cozzi**, KF Foley. Stimulant and antidepressant-like effects of novel arylketones. *Soc. Neurosci. Abs., 29*, 757.11 (2003)

**NV Cozzi**, KF Foley. Methcathinone is a substrate for the serotonin uptake transporter. *Soc. Neurosci. Abs., 27*, 814.10 (2001)

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**NV Cozzi**, KF Foley. Bromine substitution at the ring 3- or 4-position of methcathinone enhances potency at serotonin uptake transporters. *Soc. Neurosci. Abs., 25*, 678.17 (1999)

**NV Cozzi**, MK Sievert, AT Shulgin, P Jacob III, AE Ruoho. Methcathinone and 2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one (methylone) selectively inhibit plasma membrane catecholamine reuptake transporters. *Soc. Neurosci. Abs., 24*, 341.8 (1998)

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A Boileau, **NV Cozzi**, P Chen, C Czajkowski. Identification of GABA- and diazepam-responsive regions of the $GABA_A$ receptor using $\gamma 2/\alpha 1$ subunit chimeras. *Soc. Neurosci. Abs., 22*, 509.3 (1996)

MH Weiler, D Katz, H.-J Lee, **NV Cozzi**, K Das Gupta. Inositol phosphate (IP) accumulation in rat neostriatal slices under conditions used to monitor neurotransmitter release. *Soc. Neurosci. Abs., 17,* 173.9 (1991)

**Invited Reviews and Other Publications**

**NV Cozzi**. Psychedelic breakthroughs in neuroscience: how psychedelic drugs influenced the growth and development of psychopharmacology. *Multidisc. Assoc. Psychedelic Studies, 23 (1)*, 16-19 (2013)

Editor: *The Shulgin Index*, AT Shulgin, PF Daley, T Manning (2011). Transform Press, Berkeley, CA 94712. ISBN: 978-0-9630096-3-0

Book review: *Psychedelic Medicine: New Evidence for Hallucinogens as Treatments*, TB Roberts, MJ Winkelman, Eds. (2007) Praeger/Greenwood, Westport, CT 06880. ISBN: 0-275-99023-0

RA Sewell, M Baggott, **NV Cozzi**, R Doblin, R Forte, M Franklin, NM Goldsmith, P Goodwin, C Guillot, J Hanna, J Holmes, I Jerome, S Kumar, CD Lovett, D Merkur, J Onnie-Hay, E Peden, TB Roberts, MA Ruderman, K Sachs, TC van Veen. So you want to be a psychedelic researcher? *The Entheogen Review, 15*, 41-47 (2006)

Contributing Editor: *Psychedelics* in *Alterations of Consciousness: An Empirical Analysis for Social Scientists*, I Baruss (2003). American Psychological Association Books, Washington, DC 20002. ISBN: 1-557-98993-1

**NV Cozzi**. SB-207266, an orally active 5-$HT_4$ receptor antagonist for the treatment of irritable bowel syndrome. *Curr. Res. Serotonin, 3*, 115-118 (1998)

Contributing Editor: *Peyote and the Native American Church* in *Peyote*, N Ross-Flanigan (1997). Berkeley Heights, NJ 07922. ISBN: 0-8949085-1-0

Contributing Editor: *Toxicity of Ecstasy* in *Ecstasy Reconsidered*, N Saunders (1997). Turnaround Press, London, England. ISBN: 0-9530065-0-6

**NV Cozzi**. SDZ-HTF-919, a 5-$HT_4$ receptor partial agonist for the treatment of gastrointestinal motility disorder and irritable bowel syndrome. *Curr. Drugs Serotonin ID Res. Alert, SDZ-HTF-919,* ISSN 1361 6285 (1997)

**NV Cozzi**. A review of the chemistry and pharmacology of CV-5197, a 5-$HT_2$ receptor antagonist. *Curr. Drugs Serotonin ID Res. Alert, CV-5197,* ISSN 1361 6285 (1997)

**NV Cozzi**. Effects of water filtration on marijuana smoke: a literature review. *Multidisc. Assoc. Psychedelic Studies, 4, (2),* 4-6 (1993)

SERVICE

**Peer reviewer for the following scientific journals:**
*Archives of Toxicology*
*Bioorganic & Medicinal Chemistry*
*Bioorganic & Medicinal Chemistry Letters*
*CNS Neuroscience & Therapeutics*
*Drug Testing and Analysis*
*Journal of Neurochemistry*
*Journal of Neural Transmission*
*Psychopharmacology*

**Educational Policy Council** **2007 – 2010**
University of Wisconsin School of Medicine and Public Health

**Year 2 Course Directors' Committee for the accreditation report to the Liaison Committee on Medical Education (LCME)** **2009**
University of Wisconsin School of Medicine and Public Health

**Medical Students Committee report to the Liaison Committee on Medical Education (LCME)** **2009**
University of Wisconsin School of Medicine and Public Health

**Year 2 Grading Subcommittee co-chair, Educational Policy Council** **2009**
University of Wisconsin School of Medicine and Public Health

**Year 2 Curriculum Steering Committee** **2008 – 2009**
University of Wisconsin School of Medicine and Public Health

**Research Proposal Reviewer** **2001**
Dept. of Veterans Affairs, Office of External Reviews, Neurobiology-D
VA Palo Alto Healthcare System-Livermore Division, Livermore, CA

**Neuroscience Steering Committee** **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

**Neuroscience Symposium Organizing Committee** **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

**Neuroscience Doctoral Program Curriculum Committee** **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

**United States Pharmacopeial Convention (USP)** **2000**
Quinquennial Meeting 2000 Alternate Delegate

**Consulting Editor***: Journal of Drug Education and Awareness* **1999 – 2004**

**Telemedicine Distance Learning Committee** **1999 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

**Judge**: Carol Volkman Awards, Doctoral Student Research Day **1999 – 2000**
Brody School of Medicine, East Carolina University, Greenville, NC

## PRESENTATIONS AND PROFESSIONAL ACTIVITIES

**Hofmann's Potion** **October 20, 2014**
Presentation with Thomas Roberts, Ph.D., Bruce Sewick, M.A., Connie Littlefield
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

**Neurons to Nirvana: Understanding Psychedelic Medicines** **April 7, 2014**
Presentation with Thomas Roberts, Ph.D., Bruce Sewick, M.A., Oliver Hockenhull
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

**Psychedelics: Science and Spirit** **November 16, 2013**
Presentation, Chicago Consciousness Café, Chicago, IL

**Molecules, Mind States, and Mystical Experiences-Insights from the Study of Psychedelics** **November 16, 2013**
Presentation with Thomas Roberts, Ph.D. and Bruce Sewick, M.A.
Sponsored by the College of DuPage, Glen Ellyn, IL

**Psychedelics: Science and Spirit; DMT: The Spirit Molucule** **November 11, 2013**
Presentation with Natlie Metz, N.D. and Mitch Schultz
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

**A Psychedelic Conversation: Pharmacology, The Shulgin Farm Report, Creativity and Problem Solving** **April 29, 2013**
Presentation with Paul Daley, Ph.D. and James Fadiman, Ph.D.
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

**Indolethylamine *N*-methyltransferase expression in primate nervous tissue.** **April 19, 2013**
Presentation, Psychedelic Science 2013, Oakland, CA

**Psychedelics in the 21st Century: Pharmacology of Psychedelic Agents** **November 3, 2012**
Presentation, College of DuPage, Glen Ellyn, IL

**Psychedelics: Breakthroughs in Neuroscience, Therapeutics, and Humanitites** **May 7, 2012**
Presentation with Thomas Roberts, Ph.D. and Bruce Sewick, M.A.
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

**Molecular and Cellular Principles of Psychedelic Drug Action** **December 12, 2011**
Presentation and workshop, Cartographie Psychedelica, Oakland, CA

**Is *N,N*-Dimethyltryptamine (DMT) a Neurotransmitter?** **October 17, 2010**
Presentation, Chicago Consciousness Café, Chicago, IL

**Recent Developments in *N,N*-Dimethyltryptamine (DMT) Pharmacology** **April 16, 2010**
Presentation, Psychedelic Science in the 21st Century, San Jose, CA

**Enhancing the Professional Culture of Schools of Medicine: Relationship-Centered Care Initiative Immersion Conference II** **May 22-25, 2007**
Indiana University School of Medicine and Regenstrief Institute, Indianapolis, IN

**NIH Summit Workshop on Predictive Toxicology** — **June 15-17, 2004**
National Institutes of Health Campus, Bethesda MD

**New Ways to Skin a Cat** — **October 15, 2003**
Presentation, PhysioGenix, Wauwatosa, WI

**Discovery Channel Unsolved History Episode 23, Salem Witch Trials: Stability of ergot alkaloids under conditions of extreme heat** — **October 22, 2003**

**Discovery Channel Unsolved History Episode 21, Death of Marilyn Monroe: Pharmacokinetics of pentobarbital absorption** — **October 1, 2003**

**Another Way To Skin A Cat(hinone)** — **June 15, 2003**
Presentation, Dept. of Pharmaceutical Sciences
University of Wisconsin School of Pharmacy, Madison, WI

**Novel Monoaminergic Agents** — **October 15, 2002**
Presentation, Dept. of Cellular and Molecular Pharmacology
Chicago Medical School, Finch University of Health Sciences, North Chicago, IL

**Novel Monoaminergic Agents** — **March 8, 2002**
Presentation, Dept. of Chemistry
East Carolina University, Greenville, NC

**Novel Monoaminergic Agents** — **February 21, 2002**
Presentation, Dept. of Physiology
East Carolina University, Greenville, NC

**Probing Monoamine Transporters with Aminopropiophenones** — **October 11,, 2000**
Presentation, Dept. of Physiology
East Carolina University, Greenville, NC

**Teaching Skills for the Medical School Educator** — **May 15, 2000**
Brody School of Medicine
East Carolina University, Greenville, NC

**Mapping the Serotonin Reuptake Transporter** — **July 16, 1999**
Presentation, Dept. of Medicinal Chemistry and Dept. of Pharmacology and Toxicology
Virginia Commonwealth University, Richmond, VA

**Indan Analogues of Fenfluramine and Norfenfluramine Have Reduced Neurotoxic Potential** — **March 17, 1999**
Presentation, Dept. of Pharmacology
East Carolina University, Greenville, NC

**Mapping the Serotonin Reuptake Transporter** — **March 8, 1999**
Presentation, Dept. of Biochemistry
East Carolina University, Greenville, NC

**National Center of Leadership in Academic Medicine Personal Mentoring Program** — **1999-2000**
Protégé, Brody School of Medicine
East Carolina University, Greenville, NC

**Drugs of the Rainforest: A Pharmacological Sampler** **Octobeer 18, 1995**
Presentation, The Rainforest Pharmacy
Massachusetts College of Pharmacy, Boston, MA

**Nerve Gases: Mechanisms of Toxicity, Physiological Effects, and Antidotes** **October 15, 1991**
Presentation, Pre-Medical Student Association
University of Wisconsin Medical School, Madison, WI

**Drug Education at the College Level** **February 2-3, 1991**
Panel Member, The Bridge Conference
Stanford University, Palo Alto, CA

## PATENTS

Filtration agents and methods of use thereof. US patent number: US 20120167903 A1

## PROFESSIONAL AFFILIATIONS

American Chemical Society (Division of Medicinal Chemistry)

American Society for Pharmacology and Experimental Therapeutics (Division for Neuropharmacology)

Multidisciplinary Association for Psychedelic Studies

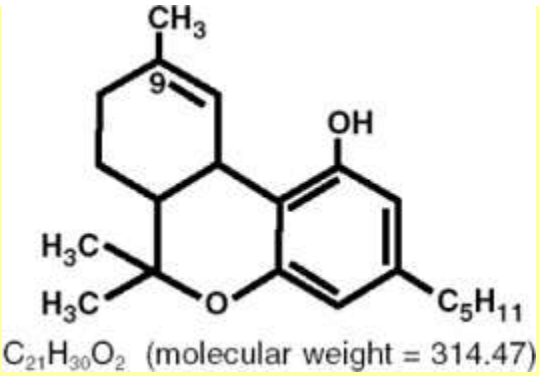
Society for Neuroscience (Division for Neuropharmacology and Neurochemistry)

**MARINOL®**
**(dronabinol) Capsules**

**Rx Only**
**CIII**

## DESCRIPTION

Dronabinol is a cannabinoid designated chemically as (6*aR-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol. Dronabinol has the following empirical and structural formulas:




$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Dronabinol, the active ingredient in MARINOL® (dronabinol) Capsules, is synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturally occurring component of *Cannabis sativa L.* (Marijuana).

Dronabinol is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

Capsules for oral administration: MARINOL Capsules is supplied as round, soft gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each MARINOL Capsule strength is formulated with the following inactive ingredients: 2.5 mg capsule contains gelatin, glycerin, sesame oil, and titanium dioxide; 5 mg capsule contains iron oxide red and iron oxide black, gelatin, glycerin, sesame oil, and titanium dioxide; 10 mg capsule contains iron oxide red and iron oxide yellow, gelatin, glycerin, sesame oil, and titanium dioxide.

## CLINICAL PHARMACOLOGY

Dronabinol is an orally active cannabinoid which, like other cannabinoids, has complex effects on the central nervous system (CNS), including central sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues. These receptors may play a role in mediating the effects of dronabinol and other cannabinoids.

### Pharmacodynamics

Dronabinol-induced sympathomimetic activity may result in tachycardia and/or conjunctival injection. Its effects on blood pressure are inconsistent, but occasional subjects have experienced orthostatic hypotension and/or syncope upon abrupt standing.

Dronabinol also demonstrates reversible effects on appetite, mood, cognition, memory, and perception. These phenomena appear to be dose-related, increasing in frequency with higher dosages, and subject to great interpatient variability.

After oral administration, dronabinol has an onset of action of approximately 0.5 to 1 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer after administration.

Tachyphylaxis and tolerance develop to some of the pharmacologic effects of dronabinol and other cannabinoids with chronic use, suggesting an indirect effect on sympathetic neurons. In a study of the pharmacodynamics of chronic dronabinol exposure, healthy male volunteers (N = 12) received 210 mg/day dronabinol, administered orally in divided doses, for 16 days. An initial tachycardia induced by dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A decrease in supine blood pressure, made worse by standing, was also observed initially. These volunteers developed tolerance to the cardiovascular and subjective adverse CNS effects of dronabinol within 12 days of treatment initiation.

Tachyphylaxis and tolerance do not, however, appear to develop to the appetite stimulant effect of MARINOL Capsules. In studies involving patients with Acquired Immune Deficiency Syndrome (AIDS), the appetite stimulant effect of MARINOL Capsules has been sustained for up to five months in clinical trials, at dosages ranging from 2.5 mg/day to 20 mg/day.

### Pharmacokinetics

***Absorption and Distribution:*** MARINOL Capsules is almost completely absorbed (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the systemic circulation. Dronabinol has a large apparent volume of distribution, approximately 10 L/kg, because of its

lipid solubility. The plasma protein binding of dronabinol and its metabolites is approximately 97%.

The elimination phase of dronabinol can be described using a two compartment model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time.

The pharmacokinetics of dronabinol after single doses (2.5, 5, and 10 mg) and multiple doses (2.5, 5, and 10 mg given twice a day; BID) have been studied in healthy women and men.

**Summary of Multiple-Dose Pharmacokinetic Parameters of Dronabinol in Healthy Volunteers (n=34; 20-45 years) under Fasted Conditions**

| Mean (SD) PK Parameter Values | | | |
|---|---|---|---|
| **BID Dose** | **Cmax ng/mL** | **Median Tmax (range), hr** | **AUC(0-12) ng•hr/mL** |
| 2.5 mg | 1.32 (0.62) | 1.00 (0.50-4.00) | 2.88 (1.57) |
| 5 mg | 2.96 (1.81) | 2.50 (0.50-4.00) | 6.16 (1.85) |
| 10 mg | 7.88 (4.54) | 1.50 (0.50-3.50) | 15.2 (5.52) |

A slight increase in dose proportionality on mean Cmax and AUC(0-12) of dronabinol was observed with increasing dose over the dose range studied.

***Metabolism:*** Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol and its principal active metabolite, 11-OH-delta-9-THC, are present in approximately equal concentrations in plasma. Concentrations of both parent drug and metabolite peak at approximately 0.5 to 4 hours after oral dosing and decline over several days. Values for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of cannabinoid distribution.

***Elimination:*** Dronabinol and its biotransformation products are excreted in both feces and urine. Biliary excretion is the major route of elimination with about half of a radio-labeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the feces.

Following single dose administration, low levels of dronabinol metabolites have been detected for more than 5 weeks in the urine and feces.

In a study of MARINOL Capsules involving AIDS patients, urinary cannabinoid/creatinine concentration ratios were studied bi-weekly over a six week period. The urinary

cannabinoid/creatinine ratio was closely correlated with dose. No increase in the cannabinoid/creatinine ratio was observed after the first two weeks of treatment, indicating that steady-state cannabinoid levels had been reached. This conclusion is consistent with predictions based on the observed terminal half-life of dronabinol.

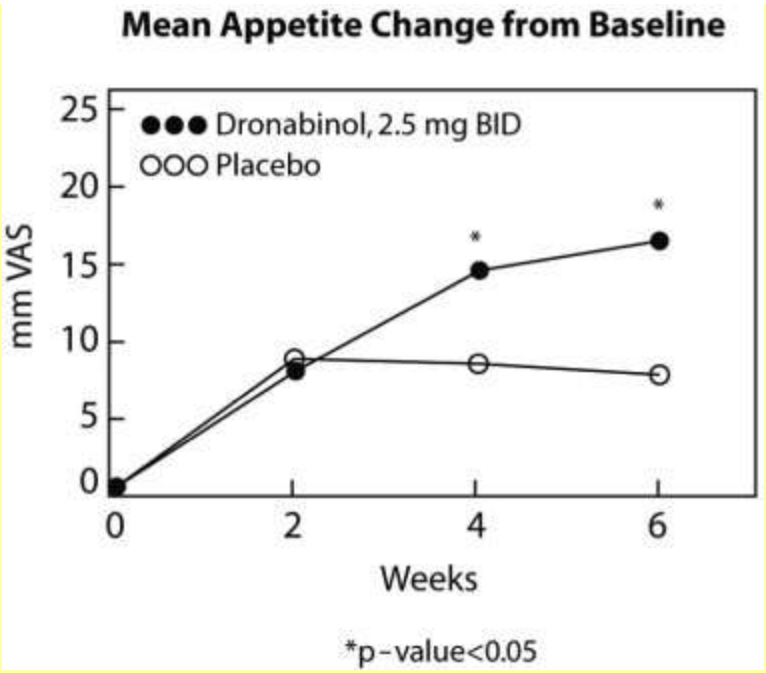
***Special Populations:*** The pharmacokinetic profile of MARINOL Capsules has not been investigated in either pediatric or geriatric patients.

**Clinical Trials**

***Appetite Stimulation:*** The appetite stimulant effect of MARINOL Capsules in the treatment of AIDS-related anorexia associated with weight loss was studied in a randomized, double-blind, placebo-controlled study involving 139 patients. The initial dosage of MARINOL Capsules in all patients was 5 mg/day, administered in doses of 2.5 mg one hour before lunch and one hour before supper. In pilot studies, early morning administration of MARINOL Capsules appeared to have been associated with an increased frequency of adverse experiences, as compared to dosing later in the day. The effect of MARINOL Capsules on appetite, weight, mood, and nausea was measured at scheduled intervals during the six-week treatment period. Side effects (feeling high, dizziness, confusion, somnolence) occurred in 13 of 72 patients (18%) at this dosage level and the dosage was reduced to 2.5 mg/day, administered as a single dose at supper or bedtime.

Of the 112 patients that completed at least 2 visits in the randomized, double-blind, placebo-controlled study, 99 patients had appetite data at 4-weeks (50 received MARINOL and 49 received placebo) and 91 patients had appetite data at 6-weeks (46 received MARINOL and 45 received placebo). A statistically significant difference between MARINOL Capsules and placebo was seen in appetite as measured by the visual analog scale at weeks 4 and 6 (see figure). Trends toward improved body weight and mood, and decreases in nausea were also seen.

After completing the 6-week study, patients were allowed to continue treatment with MARINOL Capsules in an open-label study, in which there was a sustained improvement in appetite.




***Antiemetic:*** MARINOL Capsules treatment of chemotherapy-induced emesis was evaluated in 454 patients with cancer, who received a total of 750 courses of treatment of various malignancies. The antiemetic efficacy of MARINOL Capsules was greatest in patients receiving cytotoxic therapy with MOPP for Hodgkin's and non-Hodgkin's lymphomas. MARINOL Capsules dosages ranged from 2.5 mg/day to 40 mg/day, administered in equally divided doses every four to six hours (four times daily). As indicated in the following table, escalating the MARINOL Capsules dose above 7 mg/m$^2$ increased the frequency of adverse experiences, with no additional antiemetic benefit.

**MARINOL Capsules Dose: Response Frequency and Adverse Experiences*(N = 750 treatment courses)**

| **MARINOL Capsules Dose** | **Response Frequency (%)** | | | **Adverse Events Frequency (%)** | | |
|---|---|---|---|---|---|---|
| | Complete | Partial | Poor | None | Nondysphoric | Dysphoric |
| <7 mg/m$^2$ | 36 | 32 | 32 | 23 | 65 | 12 |
| >7 mg/m$^2$ | 33 | 31 | 36 | 13 | 58 | 28 |

*Nondysphoric events consisted of drowsiness, tachycardia, etc.

Combination antiemetic therapy with MARINOL Capsules and a phenothiazine (prochlorperazine) may result in synergistic or additive antiemetic effects and attenuate the toxicities associated with each of the agents.

**INDIVIDUALIZATION OF DOSAGES**

The pharmacologic effects of MARINOL Capsules are dose-related and subject to considerable interpatient variability. Therefore, dosage individualization is critical in achieving the maximum benefit of MARINOL Capsules treatment.

***Appetite Stimulation:*** In the clinical trials, the majority of patients were treated with 5 mg/day MARINOL Capsules, although the dosages ranged from 2.5 to 20 mg/day. For an adult:

1. Begin with 2.5 mg before lunch and 2.5 mg before supper. If CNS symptoms (feeling high, dizziness, confusion, somnolence) do occur, they usually resolve in 1 to 3 days with continued dosage.
2. If CNS symptoms are severe or persistent, reduce the dose to 2.5 mg before supper. If symptoms continue to be a problem, taking the single dose in the evening or at bedtime may reduce their severity.
3. When adverse effects are absent or minimal and further therapeutic effect is desired, increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg. Although most patients respond to 2.5 mg twice daily, 10 mg twice daily has been tolerated in about half of the patients in appetite stimulation studies.

The pharmacologic effects of MARINOL Capsules are reversible upon treatment cessation.

***Antiemetic:*** Most patients respond to 5 mg three or four times daily. Dosage may be escalated during a chemotherapy cycle or at subsequent cycles, based upon initial results. Therapy should be initiated at the lowest recommended dosage and titrated to clinical response. Administration of MARINOL Capsules with phenothiazines, such as prochlorperazine, has resulted in improved efficacy as compared to either drug alone, without additional toxicity.

***Pediatrics:*** MARINOL Capsules is not recommended for AIDS-related anorexia in pediatric patients because it has not been studied in this population. The pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. Caution is recommended in prescribing MARINOL Capsules for children because of the psychoactive effects.

***Geriatrics:*** Caution is advised in prescribing MARINOL Capsules in elderly patients because they may be more sensitive to the neurological, psychoactive and postural hypotensive effects of the drug. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (See PRECAUTIONS.)

MARINOL Capsules should be used with caution when administered to elderly patients with dementia, who are at increased risk for falls as a result of their underlying disease state which may be exacerbated by the central nervous system effects of somnolence and dizziness associated with MARINOL Capsules. These patients should be monitored closely and placed on fall precautions prior to initiating MARINOL therapy. In antiemetic studies, no difference in efficacy was apparent in patients >55 years old.

**INDICATIONS AND USAGE**

MARINOL Capsules is indicated for the treatment of:

1. anorexia associated with weight loss in patients with AIDS; and
2. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

**CONTRAINDICATIONS**

MARINOL Capsules is contraindicated in any patient who has a known sensitivity to MARINOL Capsules or any of its ingredients. It contains cannabinoid and sesame oil and should never be used by patients allergic to these substances.

**WARNINGS**

Patients receiving treatment with MARINOL Capsules should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

**PRECAUTIONS**

**General:** The risk/benefit ratio of MARINOL Capsules use should be carefully evaluated in patients with the following medical conditions because of individual variation in response and tolerance to the effects of MARINOL Capsules.

Seizure and seizure-like activity have been reported in patients receiving MARINOL Capsules during marketed use of the drug and in clinical trials. (See **ADVERSE REACTIONS** and **OVERDOSAGE.**) MARINOL Capsules should be used with caution in patients with a history of seizure disorder because MARINOL Capsules may lower the seizure threshold. A causal relationship between MARINOL Capsules and these events has not been established. MARINOL Capsules should be discontinued immediately in patients who develop seizures and medical attention should be sought immediately.

MARINOL Capsules should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia. (See **CLINICAL PHARMACOLOGY.**)

MARINOL Capsules should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence, because they may be more prone to abuse MARINOL Capsules as well. Multiple substance abuse is common and marijuana, which contains the same active compound, is a frequently abused substance.

MARINOL Capsules should be used with caution and careful psychiatric monitoring in patients with mania, depression, or schizophrenia because MARINOL Capsules may exacerbate these illnesses.

MARINOL Capsules should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.

MARINOL Capsules should be used with caution in elderly patients because they may be more sensitive to the neurological, psychoactive, and postural hypotensive effects of the drug.(See **INDIVIDUALIZATION OF DOSAGES.**)

MARINOL Capsules should be used with caution in pregnant patients, nursing mothers, or pediatric patients because it has not been studied in these patient populations.

**Information for Patients:** Patients receiving treatment with MARINOL Capsules should be alerted to the potential for additive central nervous system depression if MARINOL Capsules is used concomitantly with alcohol or other CNS depressants such as benzodiazepines and barbiturates.

Patients receiving treatment with MARINOL Capsules should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

Patients using MARINOL Capsules should be advised of possible changes in mood and other adverse behavioral effects of the drug so as to avoid panic in the event of such manifestations. Patients should remain under the supervision of a responsible adult during initial use of MARINOL Capsules and following dosage adjustments.

**Drug Interactions:** In studies involving patients with AIDS and/or cancer, MARINOL Capsules has been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective

agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions. Although no drug/drug interactions were discovered during the clinical trials of MARINOL Capsules, cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein-bound drugs. Although this displacement has not been confirmed *in vivo*, practitioners should monitor patients for a change in dosage requirements when administering dronabinol to patients receiving other highly protein-bound drugs. Published reports of drug/drug interactions involving cannabinoids are summarized in the following table.

| CONCOMITANT DRUG | CLINICAL EFFECT(S) |
|---|---|
| Amphetamines, cocaine, other sympathomimetic agents | Additive hypertension, tachycardia, possibly cardiotoxicity |
| Atropine, scopolamine, antihistamines, other anticholinergic agents | Additive or super-additive tachycardia, drowsiness |
| Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants | Additive tachycardia, hypertension, drowsiness |
| Barbiturates, benzodiazepines, ethanol, lithium, opioids, buspirone, antihistamines, muscle relaxants, other CNS depressants | Additive drowsiness and CNS depression |
| Disulfiram | A reversible hypomanic reaction was reported in a 28 y/o man who smoked marijuana; confirmed by dechallenge and rechallenge |
| Fluoxetine | A 21 y/o female with depression and bulimia receiving 20 mg/day fluoxetine X 4 wks became hypomanic after smoking marijuana; symptoms resolved after 4 days |
| Antipyrine, barbiturates | Decreased clearance of these agents, presumably via competitive inhibition of metabolism |
| Theophylline | Increased theophylline metabolism reported with smoking of marijuana; effect similar to that following smoking tobacco |

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies in mice and rats have been conducted under the US National Toxicology Program (NTP). In the 2-year carcinogenicity study in rats, there was no evidence of carcinogenicity at doses up to 50 mg/kg/day, about 20 times the maximum recommended human dose on a body surface area basis. In the 2-year carcinogenicity study in mice, treatment with dronabinol at 125 mg/kg/day, about 25 times the maximum recommended human dose on a body surface area basis, produced thyroid follicular cell adenoma in both male and female mice but not at 250 or 500 mg/kg/day.

Dronabinol was not genotoxic in the Ames tests, the *in vitro* chromosomal aberration test in Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. It, however, produced a weak positive response in a sister chromatid exchange test in Chinese hamster ovary cells.

In a long-term study (77 days) in rats, oral administration of dronabinol at doses of 30 to 150 $mg/m^2$, equivalent to 0.3 to 1.5 times maximum recommended human dose (MRHD) of 90

mg/$m^2$/day in cancer patients or 2 to 10 times MRHD of 15 mg/$m^2$/day in AIDS patients, reduced ventral prostate, seminal vesicle and epididymal weights and caused a decrease in seminal fluid volume. Decreases in spermatogenesis, number of developing germ cells, and number of Leydig cells in the testis were also observed. However, sperm count, mating success and testosterone levels were not affected. The significance of these animal findings in humans is not known.

**Pregnancy:** Pregnancy Category C. Reproduction studies with dronabinol have been performed in mice at 15 to 450 mg/$m^2$, equivalent to 0.2 to 5 times maximum recommended human dose (MRHD) of 90 mg/$m^2$/day in cancer patients or 1 to 30 times MRHD of 15 mg/$m^2$/day in AIDS patients, and in rats at 74 to 295 mg/$m^2$ (equivalent to 0.8 to 3 times MRHD of 90 mg/$m^2$ in cancer patients or 5 to 20 times MRHD of 15 mg/$m^2$/day in AIDS patients). These studies have revealed no evidence of teratogenicity due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions. Such effects were dose dependent and less apparent at lower doses which produced less maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Dronabinol should be used only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Use of MARINOL Capsules is not recommended in nursing mothers since, in addition to the secretion of HIV virus in breast milk, dronabinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.

**Geriatric Use:** Clinical studies of MARINOL Capsules in AIDS and cancer patients did not include the sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of falls, decreased hepatic, renal, or cardiac function, increased sensitivity to psychoactive effects and of concomitant disease or other drug therapy.

**ADVERSE REACTIONS**

Adverse experiences information summarized in the tables below was derived from well-controlled clinical trials conducted in the US and US territories involving 474 patients exposed to MARINOL Capsules. Studies of AIDS-related weight loss included 157 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo. Studies of different durations were combined by considering the first occurrence of events during the first 28 days.

Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving dronabinol and 68 receiving placebo.

A cannabinoid dose-related "high" (easy laughing, elation and heightened awareness) has been reported by patients receiving MARINOL Capsules in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%). (See **Clinical Trials.** )

The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving MARINOL Capsules. About 25% of patients reported a minor CNS adverse event during the first 2 weeks and about 4% reported such an event each week for the next 6 weeks thereafter.

**PROBABLY CAUSALLY RELATED: Incidence greater than 1%.**

Rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317). Rates were generally higher in the anti-emetic use (given in parentheses).

| |
|---|
| *Body as a whole:* Asthenia.<br>*Cardiovascular:* Palpitations, tachycardia, vasodilation/facial flush.<br>*Digestive:* Abdominal pain*, nausea*, vomiting*.<br>*Nervous system:* (Amnesia), anxiety/nervousness, (ataxia), confusion, depersonalization, dizziness*, euphoria*, (hallucination), paranoid reaction*, somnolence*, thinking abnormal*. |
| *Incidence of events 3% to 10% |

**PROBABLY CAUSALLY RELATED: Incidence less than 1%.**

Event rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317).

| |
|---|
| *Cardiovascular:* Conjunctivitis*, hypotension*.<br>*Digestive:* Diarrhea*, fecal incontinence.<br>*Musculoskeletal:* Myalgias.<br>*Nervous system:* Depression, nightmares, speech difficulties, tinnitus.<br>*Skin and Appendages:* Flushing*.<br>*Special senses:* Vision difficulties. |
| *Incidence of events 0.3% to 1% |

**CAUSAL RELATIONSHIP UNKNOWN: Incidence less than 1%.**

The clinical significance of the association of these events with MARINOL Capsules treatment is unknown, but they are reported as alerting information for the clinician.

| |
|---|
| *Body as a whole:* Chills, headache, malaise.<br>*Digestive:* Anorexia, hepatic enzyme elevation.<br>*Respiratory:* Cough, rhinitis, sinusitis.<br>*Skin and Appendages:* Sweating. |

**Postmarketing Experience**

Seizure and seizure-like activity have been reported in patients receiving MARINOL Capsules during marketed use of the drug and in clinical trials. (See **PRECAUTIONS and OVERDOSAGE.**) **Reports of fatigue have also been received.** A causal relationship between MARINOL Capsules and these events has not been established.

**DRUG ABUSE AND DEPENDENCE**

MARINOL Capsules is one of the psychoactive compounds present in cannabis, and is abusable and controlled [Schedule III (CIII)] under the Controlled Substances Act. Both psychological and physiological dependence have been noted in healthy individuals receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration.

Chronic abuse of cannabis has been associated with decrements in motivation, cognition, judgement, and perception. The etiology of these impairments is unknown, but may be associated with the complex process of addiction rather than an isolated effect of the drug. No such decrements in psychological, social or neurological status have been associated with the administration of MARINOL Capsules for therapeutic purposes.

In an open-label study in patients with AIDS who received MARINOL Capsules for up to five months, no abuse, diversion or systematic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse.

An abstinence syndrome has been reported after the abrupt discontinuation of dronabinol in volunteers receiving dosages of 210 mg/day for 12 to 16 consecutive days. Within 12 hours after discontinuation, these volunteers manifested symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours post-dronabinol discontinuation, withdrawal symptoms intensified to include “hot flashes”, sweating, rhinorrhea, loose stools, hiccoughs and anorexia.

These withdrawal symptoms gradually dissipated over the next 48 hours. Electroencephalographic changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of dronabinol.

**OVERDOSAGE**

Signs and symptoms following MILD MARINOL Capsules intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include memory impairment,

depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

The estimated lethal human dose of intravenous dronabinol is 30 mg/kg (2100 mg/ 70 kg). Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg (28 mg/70 kg) of MARINOL Capsules.

**Management:** A potentially serious oral ingestion, if recent, should be managed with gut decontamination. In unconscious patients with a secure airway, instill activated charcoal (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal. Patients experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet area and offered reassurance. Benzodiazepines (5 to 10 mg diazepam *po*) may be used for treatment of extreme agitation. Hypotension usually responds to Trendelenburg position and IV fluids. Pressors are rarely required.

## DOSAGE AND ADMINISTRATION

**Appetite Stimulation:** Initially, 2.5 mg MARINOL Capsules should be administered orally twice daily (b.i.d.), before lunch and supper. For patients unable to tolerate this 5 mg/day dosage of MARINOL Capsules, the dosage can be reduced to 2.5 mg/day, administered as a single dose in the evening or at bedtime. If clinically indicated and in the absence of significant adverse effects, the dosage may be gradually increased to a maximum of 20 mg/day MARINOL Capsules, administered in divided oral doses. Caution should be exercised in escalating the dosage of MARINOL Capsules because of the increased frequency of dose-related adverse experiences at higher dosages. (See **PRECAUTIONS.**)

**Antiemetic:** MARINOL Capsules is best administered at an initial dose of 5 mg/$m^2$, given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy is given, for a total of 4 to 6 doses/day. Should the 5 mg/$m^2$ dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/$m^2$ increments to a maximum of 15 mg/$m^2$ per dose. Caution should be exercised in dose escalation, however, as the incidence of disturbing psychiatric symptoms increases significantly at maximum dose. (See **PRECAUTIONS.**)

**Storage Conditions**

**MARINOL Capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) and alternatively could be stored in a refrigerator. Protect from freezing.**

**HOW SUPPLIED**

**MARINOL Capsules (dronabinol solution in sesame oil in soft gelatin capsules)**

**2.5 mg white capsules (Identified UM).**
NDC 0051-0021-21 (Bottle of 60 capsules).

**5 mg dark brown capsules (Identified UM).**
NDC 0051-0022-21 (Bottle of 60 capsules).

**10 mg orange capsules (Identified UM).**
NDC 0051-0023-21 (Bottle of 60 capsules).

**Manufactured by:**
Banner Pharmacaps, Inc.
High Point, NC 27265

For:
AbbVie Inc.
North Chicago, IL 60064, U.S.A.



**PATIENT INFORMATION**

**MARINOL® (dronabinol)**
**Capsules**
**2.5 mg, 5 mg, 10 mg**
**for use in the loss of appetite**
**associated with weight loss**
**in patients with AIDS.**

**IMPORTANT**

YOUR DOCTOR HAS PRESCRIBED THIS DRUG FOR YOUR USE ONLY. DO NOT LET ANYONE ELSE USE IT.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN AND PETS. If a child puts a capsule in his or her mouth or swallows MARINOL® Capsules, take the medicine away from the child and contact a poison control center immediately, or contact a doctor immediately.

Do not drive a car or operate machinery until you know how MARINOL Capsules affects you. While taking MARINOL Capsules, do not drink alcohol, smoke marijuana, or take other drugs that have an effect on the central nervous system (such as sedatives or hypnotics). Unless advised by your doctor, do not use MARINOL Capsules if you are pregnant or nursing.

**INTRODUCTION**

This leaflet provides a summary of information about MARINOL Capsules. Please read it and keep it with your medicines in case you need to look at it again. Ask your doctor, nurse, or pharmacist if you have any questions.

MARINOL Capsules contains man-made dronabinol (THC). Dronabinol also occurs naturally, and has been extracted from *Cannabis sativa L*. (marijuana).

**PRECAUTIONS**

Be sure to tell your doctor if you:

- have or had heart disease
- have or had cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia
- have current or a history of drug abuse
- have current or a history of alcohol abuse
- have or had mental health problems (mania, depression, schizophrenia)
- have a history of seizure disorder and/or seizure-like activity
- have allergies to drugs
- are pregnant or nursing, or become pregnant

If you become pregnant while taking MARINOL Capsules, stop using it until you have talked to your doctor.

MARINOL Capsules should be used with caution in children because it has not been studied in children.

MARINOL Capsules should be used with caution in elderly patients because they may be more sensitive to the neurological, psychoactive, and postural hypotensive effects of the drug.

MARINOL Capsules can dangerously interact with alcohol and with other drugs that have an effect on the central nervous system (such as Valium, Librium, Xanax, Seconal, Nembutal, or Phenobarbital).

Do not drive or operate machinery until you are sure how MARINOL Capsules affects you and you are able to perform safely.

You may experience changes in mood or have other effects when first taking MARINOL Capsules. Be sure that there is a responsible person nearby when you first take MARINOL Capsules or when there is an adjustment in your dose.

Tell your doctor if you are taking any other prescription or nonprescription medicines.

Do not smoke marijuana while using MARINOL Capsules. This can cause an overdose.

## INFORMATION ABOUT USING MARINOL CAPSULES

**Introduction**

Eating a nutritionally balanced diet is fundamental for all stages of life. For persons living with Human Immunodeficiency Virus (HIV); it's especially important to ensure an adequate diet to maintain an ideal weight and good nutritional status. There is some indication that optimal nutrition can help maintain the integrity of the immune system, and an adequate diet will allow you to better withstand the diseases associated with an AIDS diagnosis.

Many conditions, frequently interrelated, may cause a loss of appetite. Chewing and swallowing may become difficult or painful, due to inflammation or sores in your mouth and throat.

You may experience intermittent diarrhea or overall physical discomfort associated with AIDS. Sometimes, shopping for food and preparing adequate meals may drain your energy and desire to eat. Mental depression also may result in a loss of your appetite, or you simply may grow increasingly frustrated with repeated eating problems.

A loss of appetite may occur at various times during illness associated with HIV infection. It often leads to the selection of an inadequate diet. Because a poor nutrient intake can result in weight loss and malnutrition, it's important to learn to recognize and handle a temporary loss of your appetite.

Your doctor may prescribe an appetite stimulant such as MARINOL Capsules. MARINOL Capsules should be taken exactly as directed by your doctor, and indicated on the prescription label. You will most likely start therapy by taking one white capsule (2.5 mg) of MARINOL Capsules twice daily, before lunch and supper. Your doctor may adjust your MARINOL Capsules dosage if needed to maximize its effect or to decrease any side effects.

If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double your dose. MARINOL Capsules must be swallowed whole to work effectively. Do not crush or chew the capsules.

It is important not to take sedatives, hypnotics, other mind altering substances, or alcohol, while taking MARINOL Capsules without notifying your health care givers (physician, pharmacists and nurses). Do not drive or attempt other activities requiring full alertness while taking MARINOL Capsules. Your doctor will advise when you may resume these activities.

Your doctor and pharmacist should be made aware of any other prescription medications or over-the-counter products you may be taking, as they could affect the way you respond to MARINOL Capsules.

Remember to keep this and all other medication out of the reach of children.

Increasing your appetite is only the first step in improving your nutritional status. How, what, and when you eat are also very important.

**How to Eat**

The purpose of consuming an adequate diet, even at times when you don't feel like eating, is to maintain an ideal weight and good nutritional status. Key to an adequate diet for HIV-infected individuals are foods dense in calories and nutrients. In other words, when you find it difficult to eat, make the most of what you do consume by selecting foods that provide many calories or nutrients in each mouthful.

Try some of the following ideas to boost your food intake. Keep in mind the foods you previously may have limited in your diet, especially those higher in fat, now can provide a significant source of calories. Enjoy an ice cream sundae frequently.

Cool or cold foods can dull pain from mouth and throat sores; popsicles may even numb your mouth prior to eating a larger meal. The cooler temperatures also diminish the aroma of unappetizing food.

Blend one cup of nonfat dry milk powder with one quart of whole milk. Refrigerate and use "double strength" milk for all traditional uses (puddings, cereal, shakes, soups).

Foods with a softer consistency, such as applesauce, may aid swallowing. Creamed sauces or gravies also moisten food to encourage swallowing.

Creating an appetizing meal involves more than just food. Try to eat in a pleasant atmosphere – sit in a comfortable chair, use a tablecloth and china, invite a friend to share your meal.

**What to Eat**

Planning ahead is one of the most effective ways to deal with a loss of appetite. Stock up on staple foods, particularly those high in calories and protein, so they're available when you need them. Include favorite foods on your shopping list. Also consider these protein and nutrient dense foods:

- Nonfat dry milk powder
- Powdered breakfast drinks
- Peanut butter and jelly
- Pudding cups
- "Trail mix" (dried fruit, nuts, cereals)
- Creamed soups
- Canned (or frozen) fruit in heavy syrup
- Canned tuna, chicken or other sandwich spreads
- Boxed macaroni and cheese

In addition to staples, refrigerated and frozen foods contribute important nutrients to an adequate diet. Several key choices, high in protein and calories, are listed below:

- Yogurt
- Cheeses
- Cold cuts, beef and poultry
- Cottage cheese
- Ice cream and sherbet
- Popsicles or pudding pops

- Hard cooked eggs or pasteurized eggs*

*Raw or undercooked cracked eggs pose danger of *Salmonella*. The compromised immune function of persons with AIDS places them at greater than average risk from *Salmonella* infection.

Commercial food supplements are also available to boost your caloric and nutrient intake. Offered in a variety of flavors and textures, these products supply a concentrated source of calories and protein. You may want to ask your treatment provider for more information about supplements. You may also request a referral to a registered dietitian who can provide individualized dietary recommendations to you.

**When to Eat**

"Nutritious" meals can be eaten three times a day, but frequent, small snacks or meals can help you consume the calories and protein you need without feeling full from a large meal. Eat when you feel hungry, using modern technology, including your microwave, to quickly prepare a nutritious snack or meal.

**Storage Instructions**

The best place to store MARINOL Capsules is in a cool place (46-59°F; 8-15°C) or in the refrigerator. Be careful that the capsules don't freeze. Heat or moisture may cause your MARINOL Capsules to break down or stick together, so keep your medicine away from heat and direct light, and potentially damp places like in the bathroom or near the kitchen sink.

**If You Are Taking Medicines**

MARINOL Capsules use may change the effect of other medicines. It is important to tell your doctor about all the medicines you are taking including all non-prescription medication.

**What to Watch For (Adverse Effects)**

You should not smoke marijuana while using MARINOL Capsules. It is possible to get too much dronabinol (an overdose), especially if you use MARINOL Capsules and smoke marijuana at the same time. Signs of a mild overdose would include drowsiness, euphoria, heightened sensory awareness, altered time perception, red eyes, dry mouth and rapid heart rate (tachycardia). Moderate overdosage would produce memory problems, depersonalization, mood alteration, urinary retention, and constipation. Severe overdosage would lead to decreased motor coordination, lethargy, slurred speech, and dizziness when standing up too fast (postural hypotension).

An overdose might cause you to faint.

**If You Have Problems in the First Few Days**

When you first use MARINOL Capsules your body is more sensitive and you may experience dizziness, confusion, sleepiness, or a high feeling. These symptoms usually go away in 1 to 3 days with continued dosage. If these symptoms are troublesome or persist, notify your doctor at once. Your doctor may then reduce the dose to one capsule before supper, or later in the evening, or even at bedtime.

**What to Do When Problems Occur**

**IF YOU NOTICE ANY WORRISOME SYMPTOMS OR PROBLEMS, STOP THE MARINOL CAPSULES AND CALL YOUR DOCTOR AT ONCE.**

Manufactured by:
Banner Pharmacaps, Inc.
High Point, NC 27265

For:
AbbVie Inc.
North Chicago, IL 60064, U.S.A.

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